Vestibular Schwannoma Treatment: Patients' Perceptions and Outcomes

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Voor MarieLouise en Pepijn

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Chapter 1

Introduction and outline of the thesis

The most common benign tumor of the cerebellopontine angle is variously known as acoustic neurinoma, acoustic neuroma or acoustic schwannoma and accounts for 6% to 8% of all intracranial neoplasms. The nomenclature of the tumor, however, changes over time. Because the tumor most commonly arises from the superior vestibular nerve instead of the acoustic division of the eight cranial nerve and is composed of the Schwann cells in the neurilemma, the more adequate term "vestibular schwannoma" (VS) has been proposed and will therefore be used throughout this thesis (1,2).

The incidence rate of VS now varies between 1-1.5 per 100,000/ year, although the widespread use of magnetic resonance imaging (MRI) may lead to detection of more tumors and an increase of the incidence rate (3-5). VS are usually found in adults with a mean age ranging from 46 to 58 and with female predilection in several series (6-8). They occur in two different clinical presentations. The unilateral sporadic vestibular schwannomas, which are not hereditary, consist of about 95% of cases. Approximately 5% of all patients with vestibular schwannomas have neurofibromatosis type two (NF2), which occurs in 1 per 50,000 of the general population and which is generally found in children or young adults (9). NF2 is autosomal dominant and is characterized by the development of bilateral vestibular schwannomas, peripheral schwannomas, meningiomas and presenile lens opacities. The NF2 gene has been mapped to chromosome 22 and is thought to be a 'tumor suppressor gene'. Like other tumor suppressor genes (such as p53), the normal function of the NF2 gene is to stall cell growth and division, ensuring that cells do not divide uncontrollably. A mutation in the NF2 gene impairs its function, and accounts for the clinical symptoms observed in NF2 patients. There are major differences in both clinical presentation as well as choice of treatment between the unilateral and bilateral tumors and therefore this thesis will be limited to the unilateral sporadic vestibular schwannomas.

Vestibular schwannomas usually cause unilateral hearing loss, tinnitus and sometimes dizziness or vertigo. In larger tumors unsteadiness, trigeminal symptoms and long tract symptoms may arise. However, symptoms due to affected lower cranial nerves are rarely seen. In very large tumors, brain stem compression, obstructive hydrocephalus and increase of intracranial pressure can also be observed. For many years, VS was diagnosed using standard audiometry together with auditory brain stem evoked responses (ABRs), which is a sensitive indicator of retrocochlear pathology, and computer tomography of the internal auditory canal. This method could demonstrate a widening of the porus or when contrast enhanced, a VS

extending into the cerebellopontine angle (CPA). Nowadays, contrast enhanced MRI using T1-weighted images, is the gold standard for diagnosing VS and tumors as small as 2-3 mm can be detected (10).

Vestibular schwannoma treatment

Microsurgery

More than a century after Eduard Sandifort (1742-1814), professor of anatomy at the University of Leiden, described the first presumptive case of VS, Sir Charles Balance (1856-1936) successfully operated on a VS for the first time in 1894 (11,12). In his surgical report, he described the difficulties of getting his index finger around the tumor to achieve removal. But the patient was still alive after surgery albeit with a fifth and seventh nerve palsy.

Several decades later, the treatment of VS had been further developed, but still with high operative mortality: for instance, at the 1913 International Conference of Medicine in London, the perioperative mortality in the major centers was reported at 78% and most survivors experienced significant postoperative morbidity (13). However, surgical techniques continued to evolve with the introduction of different surgical approaches, better anesthesia and use of antibiotics. One of the greatest improvements of that time was probably the introduction of the operating microscope by the otologist William House in 1961. As of that time, the VS field was no longer dominated by neurosurgeons like Harvey Cushing or Walter Dandy. Together with William Hitselberger, also a renowned neurosurgeon, House could further develop surgical approaches like the translabyrinthine (TL) and middle fossa (MF) approach. They became a unique surgical team and were thereby the founders of the close cooperation between otologists and neurosurgeons in the treatment of VS, a cooperation which still exists today. In 1968, House reported on 141 patients with a 72% facial nerve preservation rate. In 1978, in a subsequent series of 500 VS patients, the facial nerve was anatomically preserved in 96.6% of these patients (14,15). With the use of new surgical approaches and more recently intraoperative facial nerve monitoring, it was not only possible to save the life of a patient suffering from VS, but the tumor could now be removed more radically. Moreover, important structures such as the facial nerve and inner ear could also be saved.

Nowadays, the perioperative mortality has become less than 1%, with favorable cranial nerve outcomes reported by the major centers (16-22). However, despite these advances, considerable risk still exists to both facial nerve functioning and hearing. Furthermore, microsurgery may lead to complications such as postoperative intracranial haemorrhage, cerebrospinal fluid (CSF) leak and meningitis.

Radiosurgery

During the evolution of microsurgical treatment, others were working to develop new concepts for tumor management. In 1969, Lars Leksell was the first to treat vestibular schwannomas with Gamma Knife radiosurgery at the Karolinska Hospital in Stockholm, Sweden (23). He proposed the technique of focusing multiple beams of external radiation on the stereotactically defined intracranial tumor. The average of these intersecting beams results in very high doses of radiation in the tumor, but very low doses to non-target tissues along the pathway of each beam. The modern Gamma Knife consists of 201 fixed cobalt radiation sources in a fixed hemispherical array, such that all 201 photon beams are focused on a single point. The patient is stereotactically positioned in the Gamma Knife so that the intracranial tumor coincides with the isocenter of radiation. The radiation target volume is shaped conform to the intracranial tumor using beam blocking, variable collimation and multiple isocenters.

Another radiation alternative for the treatment of VS is conventional radiotherapy (24). This technique, by contrast, delivers the dose to the tumor in fractions. The dose can be targeted using stereotaxy as well as conformal techniques.

This thesis will discuss the results of radiosurgical treatment of VS using the linear accelerator (LINAC) system. In 1984, an alternative radiosurgical option, the LINAC, was first described by Betti et al (25). Since then, the precision and accuracy of the LINAC systems have been further improved and modified for the required radiosurgical application (26, 27) Most LINAC systems rely on the following basic principles: a collimated photon beam is focused on the stereotactically identified intracranial tumor. The gantry of the LINAC rotates around the patient, producing an arc of radiation focused on the tumor. The patient couch is then rotated in the horizontal plane and another arc is performed. In this manner, multiple non-coplanar arcs of radiation intersect at the target volume and produce a high target dose, with minimal radiation dose to surrounding tissue. The dose concentration method is analog to the multiple intersecting beams of cobalt radiation in the Gamma Knife

system. Again the target dose distribution can be shaped according to the tumor using variable collimation, multiple isocentres or changing the arc angles. Dose distributions are the same for LINAC based and Gamma Knife systems.

In the past, results from radiosurgical studies showed relatively impaired cranial nerve functions, which were probably caused by the higher dose of radiation to the tumor margin and higher target volumes. Moreover, at that time, radiosurgery was planned with early generation CT scans with relatively poor quality, making it more difficult to dose planning to the tumor margin. At the present time, advances in dose planning software and MR imaging together with a gradual decline in the prescribed dose of radiation have significantly improved cranial nerve outcomes, have reduced complication rates and have resulted in promising long term tumor control (28-34). However, there are some limitations to the treatment. For instance, the goal of treatment is to achieve tumor control and not removal, which means that with this technique there is no ability to relieve the mass effect of the tumor. Moreover, in order to avoid complications, lower and potentially less effective doses are required for higher tumor volumes. This limits the use of radiosurgery to the treatment of smaller tumors. Furthermore, the evidence regarding long term tumor control after low dose radiosurgery is only recently becoming available. Another limitation is the need for lifelong follow-up even after successful treatment. Despite these limitations, there is increasing evidence that radiosurgery is a safe and effective alternative therapy for vestibular schwannomas (28-30).

Observation

Technical advances such as the advent of magnetic resonance imaging (MRI) also made it possible to detect small tumors early in patients with minimal or no symptoms. With the widespread use of MRI, the relative incidence of smaller tumors has risen significantly. Moreover, increased knowledge on the natural history of these tumors shows that most VS are slow growing or do not grow at all (35,36). In a recent meta-analysis Smouha et al. found a mean growth rate of 1.9 mm/year during an observation period of 3.2 years (37). Some reports also describe spontaneous involution or rather rapid growth (38,39). As a result, experts in the field of skull base surgery have questioned the need for major skull base surgery in every case of VS. Despite advances in microsurgical treatment, patients may be left with deficits, which are not insignificant and outcomes may not automatically equate improved QoL. Other factors might also influence the decision to refrain from treatment such

as advanced age or severe comorbidity or the fact that the tumor is located at the only hearing ear. Therefore, in many centers, a more conservative approach has been proposed for small and medium-sized tumors, in which no treatment is offered to the patients, but an initial wait and scan surveillance until there is evidence of tumor progression or significant increase of symptoms (40-44). This approach has been increasingly supported in the literature and obviously has great appeal for patients. However, there are some limitations to this kind of approach of VS. The natural course of the tumor is still uncertain, for instance there are no predictive factors for tumor growth or progression of symptoms and delayed treatment in case of growth may impose greater morbidity (44). Furthermore, a wait and scan policy offers no definite treatment and necessitates a prolonged and probably lifelong follow-up.

Treatment decisions

As described above, VS patients have several treatment options including observation, microsurgery and stereotactic radiosurgery. However, the treatment of VS patients is still controversial with advocates and opponents of each modality. There is a large amount of literature supporting these three modalities, which are often separately assessed and only sometimes compared to each other. Despite this abundance, the evidence is generally no better than class III in the Cochrane classification of the quality of evidence (45). Thus, it appears that well-designed, randomized controlled studies (RCTs) are required in order to improve the quality of the evidence and compare the different modalities. However, the difficulty of such a study is that the three methods of VS management have totally different goals. The aim of microsurgery is complete tumor removal whereas radiosurgery aims to control tumor growth assuming that patients will not need additional treatment. Wait and scan offers patients tumor surveillance under the assumption that most tumors do not grow. Until now, there is no hard evidence for any of these approaches. First, there should be some consensus on the goals and success criteria of treatment of VS before RCTs can be undertaken.

In general, the choice of treatment for many patients depends on their own specific goals and on the expected results from their treatment. Before this decision, every patient must be provided with information about all available treatment options, including the advantages and disadvantages of each, as this is the basis for informed consent. Traditionally, the primary outcome measures in the evaluation

of treatment have evolved around mortality and morbidity. However, there is an increased interest concerning the impact of interventions on function and quality of life (QoL). QoL assessment may provide valuable information that is not always supplied by traditional outcome measures. It is now well recognized that treatment choices in individual patient care can be positively influenced by QoL assessment (46). QoL can not only help to determine patient preference, or compare well-being after different treatment modalities but also measure minor differences in response to treatment which may be missed by the traditional outcome measures.

Patients' perceptions

During the last 20 years, interest in patient reported outcomes (PROs) research has increased enormously, especially towards health status and health care interventions (46). Quality of life is an operationalization of PROs and represents the sum of an individual's physical, social, emotional, occupational and spiritual well-being. Defining QoL is therefore a complex matter and a comprehensive definition does not exist (47).

The World Health Organization has proposed "the individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals and expectations, standards and concerns" (48). This approach is a more broad and generic conceptualization of QoL and can be differentiated from a more specific 'health-related QoL', which concerns those aspects of people's lives that impact directly their health status or the more economic cost-effectiveness models of QoL. A widely used definition of 'health-related QoL' was proposed by Patrick and Erickson: "the value assigned to the duration of life as modified by the impairments, functional states, perceptions and social opportunities that are influenced by disease, injury, treatment or policy" (49). More recently, Schipper et al. described health-related QoL as: "the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient" (50). These functional effects are divided into three categories: physiological, psychological and social effects, which are thought to adequately represent QoL.

Some of the first aspects of QoL assessment were introduced in 1949 by Karnofsky, who used an index to evaluate treatment success in his patients. The Karnofsky Performance Status is an observer-rated measurement to assess patients on a 0-100 scale (0 for 'dead' and 100 for 'no evidence of disease, able to carry out normal

activity and to work') (51). Since that time, a number of rating scales for clinicians have been developed, especially in the cancer research field. However, over time the ratings on a patient's QoL by others were considered as 'surrogate' and patients themselves were asked to provide information concerning aspects of their QoL (46). At present, PROs are considered as a recognized measure in modern health care research.

In VS, QoL has long been a neglected area, given the quite low incidence compared with other more common diseases such as cancer. In the latter area, QoL is assessed with well-designed and validated measures and QoL has become a major outcome variable, which also affects the choice of medical management (52). However, since the beginning of the 1990s, QoL in VS has received increasing attention. One of the first studies on PRO was performed by Wiegand et al. in 832 VS patients who had joined a patient member organisation, the Acoustic Neuroma Association, after microsurgical treatment between 1973 and 1983 (53). Results showed that microsurgery has a significant impact on a patient's quality of daily life and that facial nerve dysfunction and hearing loss were the most difficult aspects to cope with postoperatively. However, the authors also recognized that one of the major limitations of their study was the patient sample itself, which consisted of operated VS patients who had joined the self-help group. On the other hand, this group may represent the majority of patients that underwent VS surgery in this period and therefore the results may still reflect an average VS population after surgery. The results of this study have led to numerous studies on the effects of microsurgery on QoL (54-63). Most of these were performed using a retrospective design and the QoL measures used were often not reliable or had not previously been used. However, some did use validated questionnaires such as the Short-Form 36 Health Survey (SF-36) or Glasgow Benefit Inventory (GBI) (60-63). They found that QoL was generally impaired after microsurgical treatment. Interestingly, facial nerve function only correlated weakly with impaired QoL whereas balance problems and hearing loss most affected quality of functioning.

Valid and reliable measures are necessary to assess QoL. A widely used and reliable measure of generic QoL is the SF-36, which has proven its reliability in a variety of diseases throughout different patient populations. It assesses QoL in 8 domains and measures physical, psychological and social well-being. However, the sensitivity of such a generic measure to otolaryngologic interventions or audiologic or vestibular symptoms has been questioned (64). Disease-specific measures have

been developed, therefore, in order to particularly assess QoL of patients with a specific disease. Unfortunately, a validated disease-specific questionnaire has not been developed specifically for VS patients yet. However, there are some studies that use validated questionnaires addressing symptoms that are typically observed in (treated) VS patients (56-59). Again, most of these studies were performed retrospectively; they generally demonstrated a negative effect of surgery on the subsequent symptoms and on QoL. Still, there is a need for validated disease-specific questionnaires, which might be combined with generic questionnaires in the future.

Until now, only a few studies report on QoL after radiosurgery or conservative treatment and reports comparing different modalities are scarce (61,65-70). When compared to microsurgical patients, patients treated with radiosurgery appear to have a better QoL outcome. For instance, in the study by Régis, a better QoL was reported after Gamma Knife surgery, but the QoL measures were not validated (67). However, Myrseth et al. found better QoL after Gamma Knife treatment when compared to microsurgical treatment using validated questionnaires (68). Surprisingly, little is known concerning QoL in untreated VS patients (71). Generally, impaired QoL is found for the three treatment modalities. However, often one can question whether the reduction is caused by the treatment, by suffering from the tumor, or by both. Both prospective studies with pretreatment QoL data or information from untreated patient samples may be valuable in answering this hypothesis.

Another interesting subject is how patients perceive their illness and how they cope with having an intracranial tumor. Given the quite solid status of QoL as an outcome measure in medicine, researchers and clinicians started examining determinants of QoL. This line of research, and its clinical application, might help to develop interventions that improve QoL. One concept that was found to contribute to variation across patients in their QoL was that of illness perceptions (72). Illness perceptions (IPs) pertain to the idiosyncratic ideas (cognitions) of patients (and physicians) regarding complaints and symptoms. They seem to play a role in the variation in QoL experienced by patients. IPs include the beliefs and attributions patients have regarding their illness and specifically regarding symptoms, causes, consequences, and the time the illness will last (73). They are assessed with questionnaires, drawings or even clay representations of an illness (74). IPs precede coping behavior, and in turn, coping determines QoL (75). IPs have been found to be relevant in virtually any physical disorders, and, increasingly in psychiatric disorders. IPs reflect the relevance and importance of how patients make sense of complaints,

illness and medical treatment – irrespective of objective medical knowledge. In this way, including IPs in QoL research strengthens the biopsychosocial model, which is particularly relevant in medical care for patients with a chronic illness. In patients with VS, IPs have not yet been studied before. Our current study, therefore, explores the relevance of IPs in patients with VS, and their contribution to, hopefully and possibly, an even better quality of care, and QoL.

Overview and aims of the present thesis

In the Netherlands, VS was previously described in a PhD thesis by Jos van Leeuwen, who reported on the diagnostic aspects and results of surgery in particular. The studies were performed at the Department of Otolaryngology at the University Hospital Nijmegen between 1980 and 1993 and van Leeuwen was one of the first who discussed the importance of QoL research after (surgical) treatment for VS (76). A more histopathological approach was described by Ernestine Stipkovits who provided more insight in the natural course of VS (35) in her PhD thesis, entitled "Vestibular schwannomas, aspects of biological behavior" at the University of Utrecht in 2000.

In Leiden, patients with VS have been treated for many years. In the past, VS patients were primarily referred to the Department of Neurosurgery of the Leiden University Medical Centre (LUMC). One of the main reasons was that patients used to be operated either via the retro-sigmoid (RS) or suboccipital approach (SO) and that the experience of the otolaryngologists in our department was generally limited to the translabyrinthine (TL) approach. However, in 1996 the Leiden Skull Base Pathology Meeting (SBP) was founded, which mainly consisted of otolaryngologists, neurosurgeons and neuroradiologists from the LUMC. This multidisciplinary meeting provided the basis for the close cooperation between otolaryngologists and neurosurgeons in VS, which still continues to evolve. Our department was not only increasingly involved in the management of these tumors but also became more skilled in the various surgical approaches such as the TL and middle fossa (MF) approach. As a result, all the three main approaches: TL, RS and MF are now widely used in our center. However, the advantages of the TL approach are increasingly recognized by both our otolaryngologists and neurosurgeons and it has now become the most frequently used approach and 'workhorse'. Furthermore, relatively new treatment options such as wait and scan or stereotactic irradiation have also made their way into our decision process over time. Nowadays, almost 1000 new VS

patients have been admitted to the LUMC and about 400 have been operated via the TL route.

Over time, our (surgical) treatment also continued to advance, because of improved techniques such as the high resolution MRI, the facial nerve monitor, CUSA aspirator and better perioperative care. As obvious as it may seem, we recognized that the treatment of any condition can only be justified when the results of treatment are better than the natural course of the disease. There is a growing debate on how VS can be best treated as it has become clear that the tumor may remain unchanged for many years. In an effort to contribute to this debate, QoL research was initiated at our department in 2001.

Our study assesses QoL in order to facilitate treatment choices in individual patient care, contributes to the determination of the best use of treatments and evaluates QoL in our VS patient population. It is likely that none of the three treatment modalities on its own is the best option for all individuals. Knowledge of the clinical and QoL effects of each of the different options can help clinicians to outline the choices available to patients and assist them in selecting which is best for them. For instance, if a VS patient has a small tumor with minimal symptoms, reasonable treatment options might be radiosurgery or wait and scan. The treatment choices available depend partly on the patient's age and comorbidity but also, to some extent, on the individual's preferences given the different QoL implications of the two treatments. Some patients may choose radiosurgery with possible surgical risks in the short term. Others will prefer no active treatment or subsequent risks and choose to evaluate their tumor periodically by MR imaging. Information on QoL in this context can be useful to both professionals and patients when considering what to expect, given certain health conditions and treatments. This kind of evidence to inform a clinician or patient comes from studies of populations of patients who are experiencing the condition or treatment (46).

This thesis describes QoL and clinical features in patients with VS at their diagnosis and after treatment with three different modalities: observation, microsurgery or radiosurgery.

Outline of the thesis

Chapter two prospectively assesses QoL together with illness perceptions (IPs) and coping behavior in a series of 90 consecutive, untreated VS patients. QoL assessment was performed at the moment of diagnosis, which enabled us to assess the burden of suffering from an (untreated) VS. The results were compared to patients with other serious or chronic illnesses (i.e. head and neck cancer patients or patients with chronic obstructive pulmonary disease) in order to assess what kind of IPs and coping behavior could be expected with these kinds of patients.

Chapter three describes a group of VS patients with small- and medium-sized tumors who were observed for almost four years. Failure of conservative treatment, tumor progression and development of symptoms such as hearing are described. QoL outcomes at baseline and at the end of follow-up are compared in those patients who were still included in our protocol. An initial conservative approach, in which the tumor is watched rather than treated, is an attractive option to many VS patients. However, there is no clarity about the natural course of the disease such as tumor growth, preservation of hearing or QoL.

Until recently, microsurgery was considered the 'gold standard' in the treatment of VS. However, at present stereotactic irradiation is increasingly becoming a first treatment option for VS. Chapter four presents clinical and QoL results of 64 patients with VS after low dose linear accelerator based (LINAC) radiosurgery. This multicenter study is performed in collaboration with the Erasmus University Medical Centre in Rotterdam. Both clinical results and QoL outcome are compared to existing results and norm populations.

Chapter five describes the effect of vertigo on QoL in 18 VS patients using generic and a disease-specific questionnaire for vertigo. Of the cochleovestibular symptoms in VS, vertigo is thought to affect QoL most (71). Vertigo may increasingly cause anxiety, depression and impaired functioning during physical and social activities and may therefore have a severe negative effect on quality of daily functioning of VS patients. Despite the significant impact on QoL, there is little evidence with regard to any interventions in VS patients with these symptoms. In an attempt to relieve patients from their vertigo and improve QoL, we performed translabyrinthine (TL) surgery and preoperative and postoperative results are evaluated.

The effects of postoperative facial nerve impairment on QoL still remain unclear. Some studies report a significant negative effect on QoL, whereas others do not.

However, it is well recognized that patients with facial nerve paralysis experience significant functional and psychological morbidity (77,78). In order to reanimate the paralyzed facial musculature after (surgical) trauma, there are various treatments, which consist of static and non-static procedures (79-83). The technique that is most frequently used involves a variation of the facial-hypoglossal nerve coaptation with or without static procedures. Chapter six presents a new variation to the facial-hypoglossal technique (FHT) to restore facial nerve paralysis as a result of (surgical) trauma. QoL and functional improvements are described and compared to results from other comparable techniques.

Facial nerve function is one of the most important factors defining success of treatment for both the patient and surgeon. In case of microsurgical treatment, the surgeon therefore may decide to leave some of the tumor in situ in order to preserve facial nerve function and maintain QoL, especially in large tumors. Intraoperative assessment of the extent of tumor removal, however, lacks objectivity. Objective assessment of the actual extent of removal documented with postoperative gadolinium enhanced magnetic resonance imaging (MRI) scans is therefore necessary, but is scarcely provided. Chapter seven examines the hypothesis that postoperative facial nerve function should be significantly better when residual tumor is deliberately left behind. We also objectively assess the extent of the removal using gadolinium-enhanced MRI scans and compare results with the extent of the removal as intraoperatively estimated by the surgeon.

Chapter eight discusses our major results and conclusions of the studies in this thesis and presents clinical implications and suggestions for future research.

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Chapter 2

Illness perceptions, coping, and quality of life in vestibular schwannoma patients at diagnosis

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Abstract

Objective: To evaluate illness perceptions, coping behavior, and quality of life in patients with vestibular schwannoma at diagnosis.

Study design: Prospective patient analysis.

Setting: University Teaching Hospital, tertiary care clinic.

Patients: Consecutive patients with vestibular schwannoma (n = 79) completed a set of questionnaires at diagnosis in order to assess psychological characteristics and quality of life.

Intervention: Diagnostic and rehabilitative.

Main outcome measures: Psychological characteristics and quality of life, measured via questionnaires focusing on illness perceptions (Illness Perception Questionnaire Revised), coping (Utrecht Coping List), and quality of life (SF-36), were compared to normative data for the general Dutch population and to data concerning patients with other illnesses.

Results: The SF-36 scores of vestibular schwannoma patients at diagnosis were significantly decreased when compared to healthy controls, patients with head and neck cancer, benign prostate hypertrophy (BPH), chronic obstructive pulmonary disease (COPD), and deaf patients. Scores for illness perceptions were in between those of patients with acute pain and chronic pain for most subscales, except illness identity, emotional representations, and illness coherence. In their coping behavior, vestibular schwannoma patients scored lower on the subscale active coping, sought less social support, and expressed their emotions less, but also showed less passive coping compared to reference values.

Conclusions: Vestibular schwannoma patients experience impaired quality of life compared to healthy controls and reference groups. Their illness perceptions are in between those of patients with acute and chronic pain, and their coping behavior is less active in general. This may have implications for clinical decision making and for optimizing interaction with patients. Changing illness perceptions and coping by means of an intervention and encouraging social support by means of patient support groups may improve quality of life in vestibular schwannoma patients.

Introduction

In modern medicine, patient-reported outcomes are increasingly viewed as central in evaluating medical care. Quality of life (QoL) is an operationalization of patient-reported outcomes and is defined as "the functional effects of an illness and its treatment, as perceived by the patient" (1). There is overwhelming evidence for the finding that objective characteristics of an illness are hardly associated with QoL. QoL seems to be analyzed mainly via social, psychological, and patient-health care provider characteristics.

The idea of illness perceptions is one such psychological characteristic (2). Illness perceptions pertain to the idiosyncratic ideas (cognitions) of patients (and physicians) regarding complaints and symptoms. They seem to play a role in the variation in QoL experienced by patients. Illness perceptions include the beliefs and attributions patients have regarding their illness and specifically regarding symptoms, causes, consequences, and the time the illness will last. This information is most often not directly asked for in a clinical setting. However, research shows that illness perceptions partly analyze the severity of disease experienced by the patient (QoL) and outcome (3,4).

Coping behavior is the behavior one shows in reaction to adversity in life, whether it is coping with illness or with something simpler such as, for example, a flat tire. It is thought that this coping behavior may affect the perception of QoL. An active coping style is associated with better QoL and better outcome, whereas a general passive coping style is associated with worse QoL and outcome. Seeking social support and expressing emotions, also part of coping behavior, have been shown to be important in achieving good QoL (5).

In current literature, an increasing amount of studies concerning other illnesses in different medical fields focus on QoL issues. Of these illnesses, several QoL reference groups were chosen on the basis of both clinical relevance and availability. In clinical practice, otorhinolaryngologists are familiar with head and neck cancer patients as well as deaf patients. Therefore, it may be interesting to see whether vestibular schwannoma (VS) patients have better or worse QoL than these 2 other patient groups. Furthermore, patients who have benign prostate hypertrophy (BPH) are similar to VS patients in that they both have a benign, slow-growing tumor that may cause quite bothersome symptoms. Chronic obstructive pulmonary disease (COPD) patients were chosen because they have a chronic disease causing many limitations and handicaps in daily life.

For the Utrecht Coping List (UCL), reference groups were chosen based on availability and comparability, apart from population norms. Patients with chronic pain were chosen because of the chronic character of their medical condition, which may be considered more chronic and thus less acute than recently diagnosed VS. Patients undergoing bone marrow transplantation were chosen because they have a serious life-threatening condition. Utrecht Coping List scores for head and neck cancer patients; deaf patients; or patients with BPH, COPD, or acute pain were not available.

As in other fields, QoL is a much studied topic in VS patients. Most studies are retrospective, and they consistently report QoL to be lower than in specified norm groups, usually posttreatment (6-16). In some of these studies, vertigo is found to be the major symptom affecting QoL (17,18). No study to date has evaluated illness perceptions or coping in VS patients (19). Very few studies have evaluated QoL in VS patients before treatment or before proposal to treatment (18,19). Therefore, the aim of this study was to evaluate QoL, illness perceptions, and coping behavior in patients with VS at diagnosis before proposal to treatment.

Materials and Methods

Patients

Between January and October 2005, 90 consecutive patients were newly diagnosed with VS. All these patients received a set of questionnaires accompanied by a letter informing them of the purpose of the study and instructions on how to complete the questionnaires. Patients were included before treatment and treatment proposal. Seventy-nine patients completed and returned the set of questionnaires (87.8%). Six refused due to personal problems, 4 did not respond, and 1 responded anonymously.

Thirty-six patients were men (45.6%), and mean age was 57.7 years (25.8-78.7 yr). According to the hearing classification system of the Committee on Hearing and Equilibrium (20), hearing was 20.5% Class A, 30.8% Class B, 23.1% Class C, and 25.6% Class D. Tinnitus was experienced by 64.6% of patients, and 38% experienced unsteadiness, defined as balance disorder. Eight of these patients and 2 others (total of 12.7%) experienced vertigo, defined as a paroxysmal spinning sensation, often with nausea and vomiting. The average duration of symptoms was 1 to 5 years. The trigeminal nerve was intact in 92.4% of patients, and all patients but 1 (98.7%) had House-Brackmann Grade I of the facial nerve. Thirty-eight percent of tumors

were strictly intracanalicular, and mean extracanalicular tumor size was 14.62 mm measured with MRI (Table 1).

Table 1. Characteristics of patients with VS.

	Responding patients (%) n = 79	**Non-responding patients (%) n = 11**
Sex, men	**36 (45.6)**	5 (45.5)
Age, yr (mean, (range))	**57.7 (25.8-78.7)**	56.9 (29.9-78.5)
Hearing		
Class A	**16 (20.5)**	2 (20)
Class B	**24 (30.8)**	3 (30)
Class C	**18 (23.1)**	4 (40)
Class D	**20 (25.6)**	1 (10)
Symptoms		
Tinnitus	**51 (64.6)**	9 (81.8)
Unsteadiness	**30 (38)**	5 (45.5)
Vertigo	**10 (12.7)**	1 (9.1)
Headache	**5 (6.3)**	0 (0.0)
Earache	**3 (3.8)**	0 (0.0)
Duration of symptoms		
0-6 mo	**15 (19.0)**	1 (9.1)
7-12 mo	**17 (21.5)**	1 (9.1)
1-2 yr	**9 (11.4)**	1 (9.1)
2-5 yr	**21 (26.6)**	5 (45.5)
5-10 yr	**7 (8.9)**	2 (18.2)
>10 yr	**10 (12.7)**	1 (9.1)
Status of cranial nerves		
N V unaffected	**73 (92.4)**	10 (90.9)
N VII unaffected (H-B I)	**78 (98.7)**	11 (100)
Unaffected	**71 (89.9)**	10 (90.9)
Tumor characteristics		
Intracanalicular	**30 (38.0)**	3 (27.3)
Size (extracanalicular), mean (SD)	**14.62 (8.36)**	14.88 (8.01)
Cystic component	**6 (7.5)**	2 (18.2)

Patient characteristics of responding and non-responding patients were similar. H-B I indicates House-Brackmann Grade I; N V, trigeminal nerve; N VII, facial nerve; SD, standard deviation.

Methods

The Medical Outcomes Study 36-Item Short Form Health Survey

The SF-36 is the most widely used questionnaire to assess QoL and has been validated and proven to be a reliable instrument to measure QoL in general (21). It consists of 36 items comprising 8 subscales of QoL. These subscales are 1) physical functioning and 2) social functioning, that is, the degree of limitations experienced in daily life physically and socially, respectively; 3) physical role limitations and 4) emotional role limitations, that is, limitations in work or other daily activities due to physical and emotional problems, respectively; 5) mental health, the degree of depression and anxiety; 6) vitality, the degree of energy and exhaustion; and 7) bodily pain and 8) general health quantify the subjective evaluation of the patient's own health status and pain. Higher scores indicate better perceived QoL. Data on patients' responses were scored according to the instructions on scoring syntax in the SF-36 manual (22). Dutch population norms are available for reference.

The Illness Perception Questionnaire Revised

The Illness Perception Questionnaire Revised (IPQ-R) consists of 3 parts measuring 1) illness identity, 2) cognitive and emotional representations, and 3) causal attributions (i.e., causes patients hold responsible for their illness), with the parts containing 28, 38, and 18 items, respectively. Answers are to be chosen from a 5-point Likert scale (strongly disagree to strongly agree) or from a yes-no scale. Scores are calculated over 8 dimensions of illness perception. These 8 dimensions are 1) illness identity, concerning the number of symptoms attributed to the illness; 2) timeline acute/chronic and 3) timeline cyclical concern strongly held beliefs regarding the chronicity or cyclical nature of the condition; 4) consequences concern the negative consequences of the condition, where higher scores represent negative beliefs; high scores on 5) personal control and 6) treatment control, reflecting the perceived controllability of the illness, and 7) illness coherence, representing personal understanding of the condition; indicate positive beliefs; high scores for 8) emotional representations correspond with a greater likelihood to seek medical care. Causal attributions are evaluated by category: psychological, risk factor, immunologic, accident, or chance. These causal attributions indicate which factors patients hold responsible for causing their illness: psychological factors, risk factors that is smoking, immunologic factors, or merely bad luck (accident or chance). Mean values for patients with various

medical disorders, including chronic pain and acute pain, for patients with head and neck cancer, and for patients with COPD are available for comparison (23-25). For deaf patients or BPH patients, IPQ-R scores were not available. Because the general population is not assumed to have an illness, there are no IPQ-R norm values for the general population. Scores of patients with chronic pain and acute pain may be used instead.

Utrecht Coping List

The UCL consists of statements concerning 7 different coping styles: active coping (disentangling the situation and purposefully working to solve the problem), seeking distraction (seeking distraction not to have to think regarding the problem), avoidance (leaving the problem to what it is or running away from it), seeking social support (seeking comfort and understanding from others), passive coping (being completely overwhelmed by the problem), expressing emotions (showing irritation and anger regarding the problem), and fostering reassuring thoughts (optimism). Of 47 statements, patients indicate whether they find these applicable to themselves on a 4-point scale ranging from "seldom or never" to "very often". Higher scores indicate greater affinity with specific coping styles. Dutch population norms are available for the general population aged 19 to 65 years, as well as for patients with chronic pain and for patients undergoing bone marrow transplantation (5,26,27).

Reference Populations

For the SF-36, reference populations consisted of patients with head and neck cancer, BPH, COPD, and deaf patients. In the reference study by Funk et al. (28), 180 head and neck cancer patients were included with a mean age of 58.9 years. Exclusion criteria were recurrent disease, cutaneous cancers, lymphomas, sarcomas, and thyroid or parathyroid tumors. Sex distribution was not mentioned, clinical American Joint Committee on Cancer stage at diagnosis was Stage I (13%), Stage II (17%), Stage III (18%), Stage IV (50%), or unknown (2%).

The study by Salinas Sanchez et al. focused on BPH in 181 men with a mean age of 68.8 years and undergoing surgery for prostate-related symptoms (29). Of these patients, 103 had objective symptoms such as urine retention.

Geijer et al. (30) conducted a study on COPD patients. The study population consisted of 395 male smokers with a mean age of 55.4 years due to a higher prevalence of COPD in men and limited study resources. Disease severity in COPD

is measured with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification. In the study population, 69.7% did not have any airflow limitation, 29.6% had mild disease (GOLD I), and 10.6% had moderate disease (GOLD II).

The SF-36 scores of 27 deaf patients were analyzed by Mo et al. (31). Postlingually deafened adult cochlear implant candidates were included, of which there were 12 men and 15 women. In 14 of these patients, the cause of deafness was unknown. The other patients had hereditary deafness, otosclerosis, meningitis, Ménière disease, trauma, or rubella.

For the IPQ-R, reference populations consisted of patients with head and neck cancer or COPD. Scharloo et al. (24) included 68 patients with head and neck cancer with a mean age of 60 years, of which 70% were men. Patients were excluded if they were mentally retarded or demented, or unable to fill in the questionnaires for other reasons. American Joint Committee on Cancer staging was I (11 patients), II (15 patients), III (12 patients), or IV (30 patients). The IPQ-R scores of 171 COPD patients were evaluated in another study by Scharloo et al. (25). Mean age of this population was 66 years, with 112 men and 59 women. Patients were excluded if they had other significant disabling diseases that would confound symptom reporting and QoL scoring. Disease severity of COPD was moderate (GOLD II) in 84 patients and severe (GOLD III) in 87 patients.

The first UCL reference population was studied by Hopman-Rock et al. (26) and consisted of 59 patients with chronic pain aged 63.7 years on average. Twenty-five percent of patients were men. Patients were excluded if they participated in another substudy of the Rotterdam study, had cognitive impairments, or were living in a home for the elderly. The second reference population consisted of 123 bone marrow transplant patients studied by Broers et al. (27). Mean age at bone marrow transplantation was 35.4 years. Of these patients, 74 were men and 49 were women. Patients were excluded if their IQ was too low or if their data were incomplete. Indications for treatment were acute leukemia (52%), chronic myelogenous leukemia (17.1%), or lymphoma (30.9%).

Statistical Analysis

Means were calculated for subscales of all questionnaires and compared with available Dutch population norms by Student's t-tests. If available, means were also compared with means of patients with comparable illnesses. Significance was calculated with a 99% confidence interval. A significance level of 0.01 was used to

adjust for multiple testing. Analyses were performed with the Statistical Package for the Social Sciences (SPSS 14.0 for Windows).

Results

In summary, when compared with patients with other illnesses, VS patients showed significantly lower QoL scores for almost all subscales except physical functioning. Mental health was only better in deaf patients and patients with COPD, whereas perceived general health was better for all patient groups except for men with BPH (Table 2).

Compared with patients with acute pain, VS patients scored significantly higher on the timeline (acute/chronic) subscale of the IPQ-R, indicating that they considered their illness to be more chronic than patients with acute pain. However, VS patients had a significantly lower sense of personal control and treatment control. They did not differ significantly in illness identity, in the belief in a cyclical character of their illness, or in emotional representations. Compared with patients with chronic pain, VS patients scored significantly lower on the timeline (acute/chronic) subscale, indicating that they considered their illness to be more acute than patients with chronic pain. Moreover, they had a significantly higher sense of treatment control and a significantly more coherent view regarding their illness. For personal control and psychological attributions, there were no significant differences in scores.

VS patients significantly thought of their illness as a more chronic problem and had a significantly greater sense of illness coherence compared with patients with recently diagnosed head and neck cancer. VS patients had significantly lower scores for emotional representations and expected their illness to have significantly less consequences to their lives compared with patients with head and neck cancer.

Patients with COPD attributed more symptoms to their illness (illness identity) and thought that their illness would be chronic and cyclical significantly more than VS patients. They considered their illness to have greater consequences to their lives and had a higher sense of personal control, whereas they had a lower sense of treatment control compared with VS patients. Higher scores on the first 5 subscales may be associated with less favorable outcomes compared with higher scores on the last 3 subscales. Regarding the cause of their illness, 23.8% of VS patients reported chance or bad luck was the cause of their illness. Most patients (52.5%) could not point out 1 specific item as a possible cause of their illness (Table 3).

Table 2. Comparison of SF-36 scores in VS patients to other populations.

SF-36	VS n = 78	DN n = 1139	HN n = 180	D n = 27	VS ♂ n = 36	BPH ♂ n = 181	COPD ♂ n = 395
PF	**78.3 (26.1)**	81.9 (23.2)	71.99 (29.22)	80.8 (18.7)	**84.2 (25.2)**	74.1 (21.6)*	86.3 (17.7)
SF	**56.1 (19.5)**	86.9 (20.5)*	70.48 (28.28)*	73.1 (26.1)*	**58.7 (20.2)**	80.5 (22.8)*	87.9 (18.4)*
PR	**31.9 (40.4)**	79.4 (35.5)*	52.22 (43.45)*	71 (40)*	**27.8 (39.1)**	57.9 (40.6)*	85.9 (29.5)*
ER	**25.4 (39.4)**	84.1 (32.3)*	60.65 (41.69)*	78.7 (34.5)*	**13 (29)**	77.4 (35.7)*	88.9 (26.9)*
MH	**63.5 (13.2)**	76.8 (18.4)*	64.69 (20.49)	76.2 (18.2)*	**65.4 (13.4)**	73.1 (21.3)	78.4 (16.4)*
VT	**53.8 (13.7)**	67.4 (19.9)*	51.58 (24.26)	58.8 (21.8)	**56.3 (14.9)**	68.9 (23.5)*	68.3 (19.2)*
BP	**62.4 (38.4)**	79.5 (25.6)*	59.38 (26.05)	75.1 (26.8)	**62.4 (40.1)**	69.8 (28.5)	83.3 (22.5)*
GH	**54.5 (15.6)**	72.7 (22.7)*	63.01 (20.71)*	72.6 (21.6)*	**52.6 (16.7)**	60.1 (19.4)	66.1 (18.8)*

Mean (standard deviation). Differences between means were tested with Student's t-tests.

*$p < 0.01$ compared with VS patients.

BP indicates bodily pain; BPH ♂, male patients with benign prostate hypertrophy (29); COPD ♂, male patients with chronic obstructive pulmonary disease (30); D, deaf patients (31); DN, Dutch population norms (22); ER, emotional role limitations; GH, general health; HN, head and neck cancer patients (28), MH, mental health; PF indicates physical functioning; PR, physical role limitations; SF, social functioning; SF-36, 36-Item Short Form Health Survey; VS, vestibular schwannoma patients; VS ♂, male VS patients; VT, vitality.

Coping styles of VS patients differed significantly from coping behavior of the average Dutch population. VS patients showed less active coping, but also less passive coping; they sought less social support; and expressed their emotions, that is, showed irritation and anger regarding problems, less compared with population norms. Compared with patients with chronic pain, VS patients were less avoiding toward problems, sought more social support, showed less passive coping, and fostered fewer reassuring thoughts. Patients undergoing bone marrow transplantation expressed their emotions significantly more than VS patients but fostered less reassuring thoughts (Table 4).

Table 3. Comparison of IPQ-R scores in VS patients to other populations.

IPQ-R	VS n = 80	AP n = 35	CP n = 63	HN n = 68	COPD n = 171
Illness identity	**2.21 (2.44)**	2.81 (1.73)	6.19 (2.81)*	2.32 (2.49)	5.62 (2.86)*
Timeline (acute/chronic)	**20.62 (3.99)**	13.4 (5.38)*	23.12 (4.41)*	17.12 (4.35)*	26.66 (4.41)*
Timeline (cyclical)	**10.59 (3.78)**	9.37 (2.58)	12.87 (3.89)*	9.92 (3.06)	12.13 (4.88)*
Consequences	**16.41 (2.05)**	14.23 (4.44)*	23.45 (3.89)*	19.43 (4.28)*	19.25 (6.05)*
Emotional representations	**15.33 (3.93)**	16.12 (4.03)	19.75 (4.15)*	19.21 (5.54)*	14.13 (7.03)
Personal control	**19.08 (2.62)**	22.94 (3.52)*	18.42 (4.01)	18.77 (3.78)	22.44 (5.89)*
Treatment control	**16.92 (2.96)**	19.43 (3.28)*	14.22 (3.36)*	17.46 (2.86)	14.29 (3.74)*
Illness coherence	**18.1 (3.6)**	9.31 (3)*	13.37 (4.78)*	15.79 (3.78)*	

Mean (standard deviation). Differences between means were tested with Student's t-tests. Higher scores on the first 5 subscales may be associated with less favorable outcomes compared with higher scores on the last 3 subscales.

*$p < 0.01$ compared with VS patients.

AP indicates patients with acute pain (23); COPD, patients with chronic obstructive pulmonary disease (25); CP, patients with chronic pain (23); HN, head and neck cancer patients (24); IPQ-R indicates Illness Perception Questionnaire Revised; VS, vestibular schwannoma patients.

Table 4. Comparison of VS UCL scores to other populations.

UCL	VS n = 79	DN n = 55	CP n = 299	BM n = 21
Active coping	**17.4 (3.9)**	19.2 (3.7)*	16.4 (4.2)	17.5 (3.3)
Seeking distraction	**16.9 (3.6)**	18.3 (3.1)	16.8 (3.9)	16 (3.7)
Avoiding	**15 (2.9)**	15.8 (3.5)	16 (3.1)*	15.3 (2.1)
Seeking social support	**12 (2.9)**	14.9 (4.2)*	10.2 (2.9)*	12.7 (3.2)
Passive coping	**9.9 (2.5)**	12.5 (2.7)*	11.7 (3.8)*	9.2 (2.4)
Expressing emotions	**4.9 (1.5)**	7 (1.8)*	5.3 (1.7)	6.1 (1.7)*
Fostering reassuring thoughts	**12.4 (2.3)**	13.2 (2.7)	13.3 (3.2)*	10.7 (1.9)*

Mean (standard deviation). Differences between means were tested with Student's t-tests.
*$p < 0.01$ compared with VS patients. CP indicates patients with chronic pain (26); DN, Dutch population norms (5); BM, bone marrow transplant patients (27); UCL, Utrecht Coping List; VS, vestibular schwannoma patients.

Discussion

As expected, on the basis of previous studies, QoL in Dutch VS patients before treatment was decreased compared with Dutch population norms (19). Because patients were included consecutively before treatment and treatment proposal, treatment modality did not induce bias in QoL, and apparently, QoL is reduced independently of treatment: microsurgery, radiosurgery, or wait and scan policy.

Surprisingly, VS patients were shown to perceive a lower QoL than all other patient groups. Even patients with recently diagnosed head and neck cancer had higher scores for QoL, whereas their life expectancy may be much shorter than that of VS patients. Keeping in mind that most VS patients (79.5%) did not have Class A hearing, it was striking that their QoL was still significantly lower than that of deaf patients before cochlear implant. Quality of life of men with another benign yet bothersome "tumor", BPH, was not similar to QoL of male VS patients. Coping with breathlessness (COPD) apparently does not decrease QoL as much as coping with VS. Apparently, VS patients are a group of patients that suffer from the moment of diagnosis.

The observation that illness perceptions of VS patients were in between those of patients with acute and chronic pain was not unexpected. Shortly after diagnosis, patients may have experienced their illness as acute in one way, whereas they may

have realized that the tumor in their head would influence their daily lives for some time. In that sense, they may have viewed their illness, albeit recently diagnosed, as chronic. Patients with head and neck cancer considered their illness less chronic, but they expected more consequences to their lives, which could possibly be explained by their altered life expectancy. Among other factors, patients with COPD differed from VS patients in a stronger illness identity and a greater sense of personal control. This could be explained by the symptoms of COPD that may be more easily related to the illness than symptoms to VS, and that behavior such as smoking or physical activity may have a direct influence on the symptoms experienced.

The most striking difference in coping behavior compared with reference values was the decrease in seeking social support and expressing emotions. This may cause a decrease in QoL because seeking less social support may probably result in receiving less social support. It was obvious that VS patients showed a more active and, thus, hopefully, more effective way of coping than patients with chronic pain. This may be explained by the duration of illness, which is much shorter in patients with newly diagnosed VS. Therefore, it may be important to ensure that coping behavior of VS patients does not diminish to the level of patients with chronic pain.

Putting this all together, VS patients experienced a decreased QoL with illness perceptions and coping behavior that could be expected with their type of illness. However, in general, the perceived QoL of VS patients was significantly lower than QoL of patients we compared it to. This demonstrates the need for a method to improve QoL in VS patients.

In patients who had myocardial infarction, it was found that interventions aimed at changing illness perceptions positively influenced outcome (32). The intervention consisted of 3 sessions. The first focused on providing information regarding the illness and explaining symptoms and terminology, as well as exploring the patients' beliefs regarding it. The second session focused on these beliefs to create a plan to decrease future symptoms and to create a greater sense of control. In the third session, this plan was evaluated, and symptoms and fears concerning recovery were discussed. Patients reported fewer symptoms 3 months after this intervention and returned to work earlier than controls.

Similar interventions may be beneficial to other groups of patients as well, such as VS patients. It is important to realize that recently diagnosed VS patients in a way experience their illness as acute probably because they have just been diagnosed with a new illness. However, in another way, they experience their illness as chronic

perhaps because they realize that it will not be cured within a short period of time. This may call for a different approach to the VS patient than to the patient who has acute myocardial infarction when implementing a change in ilness perceptions.

Because of the previously observed relationship between QoL and coping, that is, seeking social support, it may be expected that stimulating patients to join patient support groups and patient societies may be beneficial to VS patients, especially those lacking social support. Sharing concerns and experiences may ameliorate QoL and perhaps change illness perceptions in such a way that patients exhibit more optimism and develop more problem-focused coping and seek social support.

Questionnaires may be helpful to the clinician in pinpointing a more-than-average decreased QoL, adverse illness perceptions, and suboptimal coping behavior. The clinician may be able to intervene and anticipate on this decreased QoL even before treatment by means of adjustment of treatment proposal, and both pretreatment and posttreatment, by offering extra care and attention when needed, for example, in the form of social workers. Assessing QoL via a concise questionnaire adds significantly to the quality of medical care. It does take a few minutes to fill out questionnaires. However, it takes (much) more time to do a blood test, let alone a more invasive biomedical diagnostic test, which not always adds any relevant extra knowledge.

Finally, this study confirms previous knowledge on diminished QoL in VS patients and adds information regarding illness perceptions and coping behavior. Our study provides clinicians with knowledge concerning the psychological factors that possibly influence QoL and, thus, outcome in VS patients. With awareness regarding this topic, we can try to improve QoL in VS patients.

Conclusion

QoL of our sample of VS patients at diagnosis, measured with SF-36, is less than that of the general population, and for most subscales, also less than the QoL of patients with head and neck cancer, deaf patients, patients with BPH, and patients with COPD. Illness perceptions are in between those of patients with acute and chronic pain and slightly more positive than those of patients with head and neck cancer and COPD.

VS patients distinguish themselves from the general Dutch population by being less active in their coping behavior. Patients undergoing bone marrow

transplantation show slightly more active behavior, whereas patients who have chronic pain show significantly less active coping behavior.

Because illness perceptions and coping, but especially QoL in VS patients, are not as good as reference values, it is worth investigating possibilities for improvement. It is important for all those taking care of VS patients, both clinically and nonclinically, to be aware of this decrease in QoL at diagnosis. According to the study of Petrie et al. (32), we may be able to improve outcome by an intervention in the field of illness perceptions. Keeping this in mind, it would be valuable to investigate the role of illness perceptions, coping, and symptoms on QoL in VS patients in a future study to evaluate the possibilities for improvement of QoL in this group of patients.

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Chapter 3

Conservative treatment of vestibular schwannoma: a follow-up study on clinical and quality of life outcome

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Abstract

Objective: To determine the natural history and long term quality of life outcome following conservative treatment for vestibular schwannoma.

Study Design: Prospective study conducted in a university-based tertiary referral centre.

Patients: A total of 70 vestibular schwannoma patients who were initially included in the wait and scan protocol between January 2002 and December 2003 were followed with a mean observation time of 43 months. All patients had small- or medium-sized tumors when they were included in the protocol. Quality of life was measured at diagnosis and at the end of follow-up in those patients who were still conservatively treated using the SF-36. The study group was characterized by non-growing small tumors and relatively stable symptoms over time.

Main outcome measures: Clinical, audiometric, radiological and quality of life results.

Results: In 44 patients (63%), growth of the tumor was not observed, and 25 (36%) tumors did grow. Of the 70 included patients, 27 patients (39%) ultimately required treatment. Forty-one patients (59%) were still conservatively treated at the end of follow-up (mean, 47 ± 16 mo). Hearing was preserved in 16 (57%) of the 28 patients with useful hearing at diagnosis. At the end of follow-up, SF-36 scores were only slightly deteriorated for almost all subscales when compared to scores at diagnosis; however, differences were statistically not significant ($p > 0.05$). There was no significant correlation between the presence of cochleovestibular symptoms and quality of life scores ($p > 0.05$).

Conclusion: Conservative observation of small vestibular schwannomas may be regarded as a reasonable management option because the majority of these tumors do not grow during an initial period of observation. Conservative treatment of this subset of patients with small, non-growing tumors does not significantly affect life functioning, as reflected in SF-36 survey data. However, hearing loss did progress in this population. Thus, patients should be counseled regarding this risk and generic quality of life measures such as the SF-36 should be used with caution in future assessments. This study emphasizes the importance of combining generic and disease-specific quality of life measures in future studies of protocols of vestibular schwannoma management.

Introduction

Traditionally, treatment of vestibular schwannomas consists of microsurgical excision or stereotactic irradiation therapy. However, conservative management has increasingly become a treatment option in appropriate cases (1-5). The criteria used for recommendation of wait and scan include the patient's age and health status, tumor size and location, hearing status, and the patient's preference. The rationale for a wait and scan policy in vestibular schwannoma (VS) is the indolent growth pattern and static presentation in most cases (6,7). Improved magnetic resonance imaging (MRI) techniques now allow for an early diagnosis and exact measurement of growth, which has led to an increased number of patients with small and minimally symptomatic tumors suitable for conservative treatment. In a recent meta-analysis on conservative management, it was stated that wait and scan may be regarded as a safe approach for selected patients because most of the observed tumors (57%) did not grow, and only a minority of patients (20%) required treatment (i.e., microsurgery or stereotactic irradiation). However, the authors also concluded that there is a lack of prospectively designed studies with a clinical, radiologic, and audiometric follow-up beyond 3 years (8).

Over the past decades, quality of life (QoL) has increasingly become an important outcome measure for both patients and clinicians when discussing treatment options for VS. Several articles have been published on the patients' perspective of what constitutes a (radio)surgical success (9-14). It is now well recognized that microsurgical treatment of VS affects the patients' QoL significantly, and a trend toward more inferior QoL has been reported after stereotactic irradiation or radiosurgery. However, patient outcomes after conservative treatment have been scarcely described, and reports are often limited by the retrospective design or poorly described reference data (13,15).

A wait and scan policy implies that VS patients have to undergo periodic MRI and clinical evaluation to assess growth or progression of symptoms at least for several years after the diagnosis. In our opinion, to have a VS can therefore be considered as a chronic illness, which may be life-threatening in some cases. So far, it remains unclear how patients experience this kind of conservative approach for intracranial tumors such as VS; the effects of this treatment on QoL over time also remain to be elucidated. In this study, therefore, our first aim was to determine the natural course of VS and to identify and follow those patients who did not require treatment over

time. Second, QoL and possible correlations with cochleovestibular symptoms were prospectively studied with a follow-up of almost 4 years.

Materials and Methods

Patients

Between January 2002 and December 2003, 82 newly diagnosed VS patients were included in our wait and scan protocol. Inclusion criteria for conservative management were minimal symptoms, small- or medium-sized tumors, advanced age, poor general health, or patient preference. Patients were excluded from the study if they had neurofibromatosis type 2 (n = 1), previous surgical, or radiosurgical therapy (n = 5). Patients who were lost to follow-up (n = 2) or had less than 2 MRIs (n = 4) were also excluded. This resulted in 70 patients (29 men and 41 women) who were included in this study; they were followed until April 2008. The clinical data were obtained from the patients' clinical charts and our prospectively generated VS database (16). Patients remained included in the wait and scan protocol if surgical or radiosurgical intervention was not required. The decision for conversion to active treatment was based on the following criteria: significant tumor progression on repeated MRI, objectively quantified hearing deterioration, or the patient's preference for active treatment (e.g., in case of increase in cochleovestibular symptoms). In case of the need for surgical treatment, the surgical approach was based on the patient's hearing and the surgeon's preference for an approach technique. Facial nerve outcome was assessed according to the House-Brackmann classification (Grades I to VI) (17). In case of radiosurgical intervention, patients received stereotactic irradiation or radiosurgery.

Neuroradiologic Assessment

All patients underwent periodic gadolinium-enhanced MRI to determine tumor size or growth. In our clinic, imaging is generally performed at 12-month intervals within the first 4 years after the diagnosis. The scanning interval after this period was dictated by the clinical status of the patient or the patients' preference regarding the duration of the interval, tumor growth rate, or size of the tumor. The duration of follow-up was defined as the interval between the first and last MRI within the observation period. Tumor size was determined using the guidelines of the

American Academy of Otolaryngology Head and Neck Surgery (AAO-HNS) (18). The extracanalicular component of the tumor was determined as follows: the maximum tumor diameter was measured on T1-weighted axial MRI images with gadolinium enhancement. The measurement was calculated parallel to the petrous bone and perpendicular to it. The size of tumors limited to the internal auditory canal was calculated on T1-weighted axial MRI images with gadolinium enhancement, and the total length of the tumor along the axis of the internal auditory canal from the porus to the fundus was measured.

Tumor growth or shrinkage was considered significant in case of an increase or decrease of 2 mm or more in comparison with the previous MRI scan, as proposed by Fucci et al. (3) and Stangerup et al. (19). The growth rate was calculated by dividing the difference in tumor size between the initial and the last available MRI scan by the overall follow-up time (in months) and by multiplying the obtained figure by 12.

Audiometric Assessment

Audiometric assessments were periodically performed during conservative management. In this study, the audiometric results were recorded at diagnosis and at last clinical evaluation. The pure-tone average (PTA) was calculated as the mean sum of 0.5, 1, 2, and 4 kHz hearing thresholds. Speech discrimination scores (SDSs) were obtained in quiet conditions using word list scoring by phonemes and recorded according to the guidelines of the AAO-HNS (18). Hearing was classified (according to AAO-HNS): Class A, PTA less than or equal to 30 and SDS greater than or equal to 70%; class B, PTA less than or equal to 50 dB and SDS greater than or equal to 50%; class C, PTA greater than 50 dB and SDS less than 50%; and class D, SDS less than 50%.

QoL Assessment

The SF-36 was used to measure QoL during the observation period. All the included patients filled out the SF-36 questionnaire at the time of their diagnosis, and the patients who were still included in the wait and scan protocol at the end of the observation period filled out the same questionnaire again (April 2008). The mean scores at time of diagnosis and at the end of the observation period were then compared with each other. Furthermore, relationships between QoL scores and cochleovestibular symptoms or change in symptoms were analyzed. The SF-36 is widely used and validated as a generic outcome measure in a variety of diseases throughout different patient populations (20, 21). It has also been extensively used

in measuring QoL in VS patients (9-16). The SF-36 assesses QoL in the following 8 domains: physical functioning, social functioning, physical role functioning, emotional role functioning, mental health, vitality, bodily pain, and general health. For each domain, there is a series of itemized questions that are scored. Each score is coded, summed, and presented on a scale of 0 to 100, where 0 implies the worst possible health status and 100 the best possible (22).

Statistical Analysis

Statisical analysis was performed using SPSS version 14.0 for Windows. The 2-tailed independent t-test was used for comparison between groups and the paired t-test for comparison within groups with a 95% level of significance ($p < 0.05$). Correlations between variables were analyzed using the Pearson correlation coefficient. Nonparametric equivalents were used in case of not normally distributed data.

Results

Clinical Results

The patients' characteristics are shown in Table 1. The overall average tumor size at presentation was 10 mm (range, 2-27 mm). There were 30 intracanalicular tumors and 40 extrameatal tumors (mean, 7 ± 2 mm and 12 ± 5 mm, respectively), and groups did not differ significantly in age or sex ($p = 0.4$ and $p = 0.6$, respectively). The presenting symptoms are shown in Table 2. Unilateral hearing loss, tinnitus, and balance problems were the 3 most common presenting symptoms. For most of the patients (64%), the duration of their (cochleovestibular) symptoms was 6 to 24 months until diagnosis. There was no significant correlation between presenting symptoms and initial tumor size or intracanalicular or extracanalicular tumors ($p = 0.4$).

Tumor Growth

In 44 (63%) patients, no tumor growth was observed during the entire observation period. In 1 (1%) patient, tumor shrinkage occurred. At a mean follow-up of 32 months (range, 11-67 mo), tumor growth occurred in 25 patients (36%). Within the group of extrameatal tumors (n = 40), 22 tumors (55%) did not grow, whereas 17 tumors (43%) did grow. In 1 tumor (2%) within the extrameatal tumor group, tumor

shrinkage was observed after 36 months of follow-up. In 8 tumors (27%) within the intracanalicular group (n = 30), tumor growth was observed, and the remaining 22 tumors (73%) did not show tumor growth. Among the extrameatal tumors, a larger number of tumors showed enlargement when compared with the intracanalicular tumors. However, this difference was statistically not significant ($p = 0.3$). The mean growth rate of the growing tumors (both intracanalicular and extrameatal) was 1.5 mm/yr, and the overall growth rate was 0.45 mm/yr. There was no significant relation between patient's age, sex, initial tumor size, or presenting symptoms and growth rate (all $p > 0.05$). Tumor growth rate also did not significantly differ between intracanalicular or extrameatal tumors ($p = 0.1$).

Table 1. Patient characteristics (n = 70).

No. of patients	70
Age at diagnosis, yr	60 (35-82)
Male/female	29: 41
Follow-up, mo	40 (11-73)
Initial tumor size, mm	10 (2-27)

Table 2. Presenting symptoms (n = 70).

Symptom	**No. of patients (%)**
Unilateral hearing loss	69 (99)
Tinnitus	38 (54)
Dizziness	31 (44)
Vertigo	18 (26)
Other*	3 (4)

*Trigeminal neuralgia, facial nerve paralysis.

Treatment Group (Failure of Conservative Management)

A total of 27 patients failed (39%) conservative management during the observation period after a mean follow-up of 31 months (median, 30 mo; range, 11-67 mo) because in these patients, microsurgery or radiosurgery was required. Patients were followed for an average of 11 months postsurgery (median, 11 mo; range, 8-12 mo). Nineteen patients (76%) underwent microsurgery and 5 patients (30%) received radiosurgery because of tumor growth. One patient (4%) with tumor

growth remained included in the wait and scan protocol (because of inconsistent tumor growth). Three patients without tumor growth, but with a significant increase in cochleovestibular symptoms during the observation period, also underwent surgical treatment. Two of these patients were operated via the translabyrinthine (TL) approach, and 1 patient underwent successful hearing preservation surgery via the middle fossa (MF) approach. The surgical outcome of these patients is presented in Table 3. Facial nerve outcome was favorable (House-Brackmann Grades I and II) in all operated patients, and there were no major postoperative complications. Two patients died during follow-up because of medical reasons not related to VS.

Table 3. Surgical outcomes of 22 primarily conservatively treated patients.

Patient	Surgical approach	Hearing function at diagnosis*	Preoperative hearing function preoperatively*	Postoperative hearing function postoperatively*
1.	TL	D	D	D
2.	TL	D	D	D
3.	TL	D	D	D
4.	TL	D	D	D
5.	TL	D	D	D
6.	TL	C	C	D
7.	TL	C	C	D
8.	TL	C	C	D
9.	TL	C	C	D
10.	TL	C	C	D
11.	TL	C	C	D
12.	TL	B	D	D
13.	TL	B	B	D
14.	TL	B	C	D
15.	TL	B	B	D
16.	TL	B	D	D
17.	TL	C	D	D
18.	TL	B	C	D
19.	TL	A	B	D
20.	TL	A	D	D
21.	TL	A	B	D
22.	MF	A	A	A

* American Academy of Otolaryngology Head and Neck Surgery hearing classification (18). TL indicates translabyrinthine surgery; MF, middle fossa surgery.

Nontreatment Group (Nonfailure of Conservative Treatment)

At the end of the observational period, a total of 41 patients (59%) were still included in the wait and scan protocol (mean, 47 ± 16 mo; range, 12-73 mo). The patients' characteristics are presented in Table 4. The overall average tumor size was 10 mm (range, 2-27 mm). There were 20 intracanalicular tumors and 21 extrameatal tumors (mean, 7 ± 3 mm and 14 ± 6 mm, respectively), and groups did not significantly differ in age or sex ($p = 0.2$ and $p = 0.4$, respectively). The presenting symptoms in these patients and subsequent symptoms at the end of the observation period are presented in Table 5. Of the presenting symptoms, hearing loss worsened in 20 (49%) of the 41 patients. Patients presenting with balance problems reported improvement of dizziness and vertigo in 5 (26%) of the 19 patients and in 5 (42%) of the 12 patients, respectively. Dizziness and vertigo worsened in 3 (16%) of the 19 patients and in 2 (17%) of the 12 patients, respectively. Symptoms in 2 patients presenting with a trigeminal neuralgia and 1 patient with a mild facial nerve paralysis did not change. There was no significant correlation between presenting symptoms or change in presenting symptoms and initial tumor size or intracanalicular or extracanalicular tumors (all $p > 0.05$). The score distribution on the SF-36 dimensions is listed in Table 6. At follow-up, the SF-36 scores of the 41 patients had slightly deteriorated compared with the scores at baseline some 4 years earlier except for social functioning, which was slightly improved. However, the SF-36 scores at follow-up did not significantly differ when compared with scores at baseline (all $p > 0.05$). Baseline and follow-up SF-36 scores did not correlate significantly with cochleovestibular symptoms or tumor size (all $p > 0.05$).

Table 4. Patient characteristics for the nontreatment group (n = 41).

No. of patients	41
Age at diagnosis, yr	63 (40-79)
Male/ female	16:25
Follow up, mo	47 (12-73)
Initial tumorsize, mm	10 (2-27)

Table 5. Presenting symptoms and change at the end of observation (n = 41).

Symptom	No. of patients (%) reporting symptoms at baseline	No. of patients reporting symptoms at follow-up		
		No change	Better	Worse
Unilateral hearing loss	41 (100)	21	0	20
Tinnitus	26 (63)	24	0	2
Dizziness	19 (46)	11	5	3
Vertigo	12 (29)	5	5	2
Other*	3 (7)	3	0	0

*Trigeminal neuralgia, facial nerve paralysis.

Table 6. Quality of life scores of the conservatively treated patients (n = 41).

	At diagnosis		End of observation	
Short Form-36 scales	Mean	SD	Mean	SD
PF	81.0	23.9	80.3	23.3
SF	74.3*	28.3	77.1*	22.7
RP	73.6	39.7	72.6	40.3
RE	82.4	31.0	78.9	33.1
MH	70.0*	15.7	69.4*	16.5
VT	66.8	15.8	63.6	18.8
BP	86.3*	18.8	84.8	18.3
GH	57.4*	18.3	56.6*	20.6

PF indicates physical functioning; SF, social functioning; RP, role-physical functioning; RE, role-emotional functioning; MH, mental health; VT, vitality; BP, bodily pain; GH, general health; SD, standard deviation; * $p < 0.05$.

Audiometric Results

At their diagnosis, 33 patients (47%) presented with useful hearing on the tumor ear (Classes A and B of the AAO-HNS classification), whereas 37 patients (53%) had no serviceable hearing on the tumor ear (Classes C and D of the AAO-HNS classification) (18). In 5 (15%) of the 33 patients with useful hearing, follow-up audiometry was not available. During the observation period, 12 patients (43%) of the remaining 28 patients within the useful hearing group lost their (useful) hearing, and in 16 patients (57%), useful hearing was maintained. Of the 12 patients who lost their

useful hearing, 4 patients lost their hearing because of TL surgery resulting in permanent hearing loss in the tumor ear. A total of 5 patients who underwent TL surgery during the observational period lost their useful hearing before the surgery was performed (Table 3). In the remaining 3 patients, useful hearing was lost during the observational period. No significant difference was found in loss of useful hearing between intracanalicular and extrameatal tumors ($p = 0.2$). Nearly half of the patients with useful hearing and with a growing tumor lost their hearing because of the TL surgery. A correlation between tumor growth and hearing loss could not be adequately interpreted because of the bias caused by the inevitable hearing loss after TL surgery.

Discussion

This study reported on 1 of the few follow-up studies in VS patients, with a set of outcome variables that encompasses clinical and QoL data. We described the natural course of VS in a prospective manner and with a focus on the long term QoL in those patients who were still conservatively treated after almost 4 years of observation.

During the observational period, the vestibular schwannomas seemed to be nongrowing in most patients (63%). This finding is in line with earlier studies in which absence of growth has been reported in 40% to 76% of cases (1-6,23-26). Furthermore, these results are underlined by the data of a recent meta-analysis performed by Smouha et al. (8); they found that in 1,345 VS patients, 57% of tumors were nongrowing, whereas 43% showed positive growth during a mean follow-up of 3.2 years. The observed nongrowth rate of 57% was likely to be overestimated according to the authors because of the relatively short duration of follow-up. Nonetheless, several studies, including our study with longer follow-up periods ranging from 3 to 7 years, still report high nongrowing tumor rates (24-26). We also observed tumor involution during the observational period in 1% of cases, which is also in line with reported tumor regression rates. The observed spontaneous involution of vestibular schwannomas may be explained by tumor necrosis caused by intratumoral thrombosis and may be part of normal involution of tumors that have reached their maximum growing potential (27). The growth patterns of VS may vary from spontaneous involution to rapid growth, and unfortunately, not many clinical or radiologic factors predicting tumor growth have been found so far. Intracanalicular

tumors are thought to display less growth than extracanalicular tumors, and younger age is associated with more rapid growth and the presence of intratumoral cysts (25,26,28). Although we observed an increased number of growing tumors in the extracanalicular tumor group compared with intracanalicular tumors, this difference was not statistically different. Other patient or tumor factors (i.e., age, presenting symptoms, tumor size) were also not significantly related to observed growth.

In the current study, failure was defined as conversion from wait and scan to active treatment, which occurred in 39% of patients. Various studies report a percentage of failure between 0 and 50% (26). As in most of these studies, our decision for definitive treatment was mostly based on significant tumor growth observed on MRI. However, in our study, not all patients with tumor growth received treatment. For instance, in 1 patient, the inconsistent tumor growth was observed for several years, and there was no increase of symptoms or deteriorated QoL. In this patient, therefore, treatment was successfully postponed. In 3 patients, however, a significant increase in cochleovestibular symptoms occurred, and finally, patients preferred to undergo microsurgical treatment. One of these patients underwent hearing preservation surgery using the MF approach, and useful hearing was postoperatively maintained (Table 3). The other 2 patients underwent TL surgery and subsequent vestibular neurectomy because of the disabling character of their vertigo. Postoperatively, there were no major complications, and facial nerve function was favorable for all 22 operated patients.

Consistent data concerning hearing loss or other cochleovestibular symptoms after conservative treatment is still scarcely found (8). We found that useful hearing was maintained in 57% of patients after almost 4 years of follow-up. However, one should be cautious while interpreting these data because in some patients, recent audiometric data were not available (15%). Furthermore, a relationship between tumor progression and hearing loss could not be established because nearly half of the patients with useful hearing and with a growing tumor lost their hearing because of the TL surgery. Other authors have reported on hearing loss in 50 to 67% of cases after conservative treatment and regardless of tumor progression (29). Studies concerning hearing preservation surgery have claimed some degree of preserved hearing in 35 to 60% of cases, and similar results are reported after radiosurgery (30). When considering these results, hearing preservation, therefore, could still be a matter of debate when discussing treatment options for small- and medium-sized vestibular schwannomas.

VS may be regarded as a chronic illness, which causes discomfort and may lead to unilateral hearing loss, tinnitus, or balance problems. Moreover, patients treated conservatively have to undergo periodic radiologic, audiometric, and clinical assessment for a prolonged period after their diagnosis. Therefore, information regarding QoL during the course of conservative treatment is of great importance for this group of patients. Of the 70 patients initially included in the wait and scan protocol, 41 patients (59%) were successfully treated with a mean follow-up of 47 months. As expected from earlier studies, conservative treatment did not significantly affect our patients' QoL (1-5,13, 15,25,26,31). We performed an observational study in a population of patients with small, nongrowing tumors for which symptoms were likely to remain stable over time. Furthermore, QoL scores seemed not to be influenced by the presenting symptoms or change in symptoms during the follow-up period. Of the main symptoms, deterioration of hearing loss was reported mostly by the patients, but the loss of hearing did not seem to affect QoL. A possible explanation might be the gradual character of the hearing loss or the fact that most patients already had nonserviceable hearing at diagnosis (21 of the 41 patients). Almost one third of patients with balance problems at diagnosis reported improvement over time, which may be explained by the gradual dysfunction of the vestibular nerve from the VS accompanied by vestibular compensation in the central nervous system. Two patients reported that their vertiginous complaints had worsened, but without significantly affecting their QoL, and therefore, they did not receive treatment yet. However, it is now well recognized that the SF-36, a widely used generic questionnaire, has limitations with respect to otolaryngologic interventions or auditory and vestibular functioning (32,33). In our opinion, the interpretation of QoL results should therefore be done with caution. When compared with other published results from our center in which QoL was measured in VS patients before treatment decision or proposal, our patients had better QoL scores (16). Again, this illustrates the patient selection in our sample.

Although this study was conducted using a prospective design, there are a number of limitations to this study of which some are already mentioned earlier. The interpretation of our QoL results is hampered by lack of data of the treated patients. We have not investigated QoL in these patients because of the relatively small patient subgroups (microsurgery and radiosurgery; n = 22 and n = 5, respectively). Patients were followed-up for almost 1 year postsurgery. We are aware that these data are preliminary, and longer and more profound follow-up is needed of the entire

cohort. Furthermore, with regard to the use of the SF-36, it should have been more preferable to combine generic with disease-specific measures of QoL. However, until now, no validated questionnaire is available for assessing VS-specific QoL. We have therefore, in our opinion, used the best methods available. We acknowledge the importance of combining generic and disease-specific QoL measures for future research projects. The results of this study may be valuable for counseling patients with small- or medium-sized vestibular schwannomas.

Conclusion

Conservative management is increasingly adopted as an initial treatment option for VS. As shown in previous reports, our study shows that conservative management of small tumors is a reasonable option because most tumors do not grow. Useful hearing was preserved in half of the patients, which is in line with existing literature. Conservative treatment does not seem to worsen the patients' QoL over time. However, in this study, patients with nongrowing small tumors and with stable cochleovestibular symptoms were prospectively followed. Of the symptoms, hearing loss deteriorated most frequently during follow-up, and QoL does not seem to meaningfully deteriorate due to hearing changes in the involved ear. However, it should be taken into account that the SF-36 has its limitations with regard to assessing QoL in otolaryngologic interventions and sensitivity to symptoms such as hearing loss or balance problems. It should therefore have been preferable to combine generic with disease-specific measures of QoL.

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Chapter 4

Quality of life and clinical outcome after radiosurgery for vestibular schwannoma

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Abstract

Objective: To assess quality of life and clinical outcome in vestibular schwannoma patients after radiosurgery with marginal tumor doses of 12 Gy.

Study Design: Retrospective study conducted in a university-based referral centre.

Patients and Methods: Seventy-two consecutive, newly-diagnosed patients with a solitary vestibular schwannoma underwent linear accelerator-based radiosurgery between 2001 and 2007, all with marginal tumor doses of 1 x 12 Gy prescribed to the 80% isodose-line. A total of 66 patients were included in the study and 64 patients (97%) filled out the SF-36. The SF-36 scores of the patients were compared with SF-36 scores of healthy controls. Local tumor control and symptoms were also studied. The median follow up between treatment and quality of life assessment measured 34 months (mean, 35 mo; range, 3-78 mo). The median imaging follow-up was 31 months (mean, 34 mo; range, 4-64 mo).

Main outcome measures: Quality of life and clinical results.

Results: The median tumor diameter was 17 mm (mean, 17 mm; range, 4-28 mm). The clinical tumor control rate was 100% after a median follow-up of 31 months (mean, 34 mo; range, 4-64 mo). The imaging control rate was 98%. None of the patients had serviceable hearing before the radiosurgery. Dizziness and tinnitus were present in 45 (70%) and 46 (72%) patients before treatment, respectively. None of the patients developed dizziness or tinnitus after treatment, but dizziness worsened in 2 (3%) and tinnitus in 3 (5%) patients. Facial nerve and trigeminal symptoms developed after treatment in 2 (3%) and 4 (6%) patients, respectively. In one patient (2%) hydrocephalus occurred. The SF-36 scores for social functioning and general health were statistically significantly lower when compared to healthy controls ($p = 0.01$ and $p = 0.001$, respectively). There was no significant correlation of the SF-36 scores and tumor size, dizziness, facial or trigeminal nerve symptoms or co-morbidity. Tinnitus inversely correlated with physical-role functioning ($p = 0.01$).

Conclusion: Vestibular schwannoma patients experience impaired quality of life after radiosurgery when compared to healthy controls. However, radiosurgical treatment for vestibular schwannoma offers good tumor control and favorable clinical outcome similar to earlier reports. There is no significant correlation between quality of life outcome and disease-related symptoms, tumor size or comorbidity.

Introduction

Over the past decades, radiosurgery has become a well-established treatment for vestibular schwannoma (VS) (1-7). The two main goals of treatment are long term tumor control and preservation of quality of life (QoL), including neurological functions. Recent studies have reported long term clinical tumor control rates up to 97-99% with low marginal doses (12-14 Gy) (3-5). Despite these advances, radiosurgical treatment of vestibular schwannoma may induce or worsen complaints such as hearing loss, tinnitus, facial nerve dysfunction, facial pain and dysbalance. Another sequelae of treatment is hydrocephalus, which may require a ventriculo-peritoneal shunt (8,9).

In VS literature, the frequency and impact of these symptoms vary considerably, but an increased awareness of QoL issues has drawn more attention to these outcomes. Most radiosurgical reports, however, mainly focus on tumor control and objective neurological deficit. More subjective effects of radiosurgery on for instance tinnitus, dizziness or balance problems are scarcely reported (3). Especially imbalance and vertigo have shown to result in an impaired QoL (10,11).

So far, little is known from the patients' perspective of what constitutes a radiosurgical success. In order to increase knowledge of the patient's perception of radiosurgical treatment of VS, we assess QoL and clinical outcome in newly-diagnosed patients with solitary VS after linear accelerator-based (LINAC) radiosurgery.

Materials and Methods

Patients

Between June 2001 and December 2007, 72 consecutive newly-diagnosed patients with unilateral VS underwent linear accelerator-based (LINAC), low-dose radiosurgery at the Erasmus University Medical Centre in Rotterdam with marginal doses of 12 Gy. Retrospective analysis of the clinical charts showed that of the 72 patients, 6 patients were deceased. It were all disease unrelated deaths: four patients died because of a primary malignancy or metastasis of a malignant tumor, one patient died of a glioblastoma and one patient passed away as a result of old age. No patients were lost to follow up. This resulted in 66 eligible patients for our study. To obtain the QoL data, all these patients received a questionnaire accompanied by a letter informing them

of the purpose of the study and instructions on how to complete the questionnaires. A total of 64 patients completed and returned the questionnaire (97%). Two patients were unwilling to participate and did not fill out the questionnaire. The patient data were obtained from the patients' clinical charts and our VS database; they are summarized in Table 1. The median age of the 64 patients was 65 years (mean, 66 yr; range, 36-84 yr) when they filled out the questionnaire. Thirty two patients (50%) were male. Follow-up was defined by the time interval between treatment and the most recent MRI scan and neurological examination. The median follow-up of the 64 patients was 31 months (mean, 34 mo; range, 4-64 mo).

Table 1. Patient characteristics (n = 64).

No. of patients	64
Age, yr (median, range)	66 (65, 36-84)
Male/female	32:32
Follow-up, mo	34 (31, 4-64)
Initial tumor size, mm	17 (17, 4-28)

Tumor characteristics

All tumor diameters were measured and volumes were calculated using the planning magnetic resonance imaging (MRI) scan. The median tumor diameter was 17 mm (mean, 17 mm; range, 4-28 mm) and the median tumor volume was 2.2 cm^3 (mean, 2.2 cm^3; range, 0.1-11.4 cm^3).

Local tumor control was assessed in two ways. First, by imaging; radiological tumor control was defined as an increase in tumor diameter of less than 2 mm in any direction. A 2 mm difference seems appropriate because of the variation in voxel size and scan angle/head position during MRI. Second, by final clinical outcome; local control was defined as freedom from surgical resection.

Radiosurgical treatment

Patient immobilization was provided by the Brown-Robert-Wells stereotactic coordinate headframe from Radionics (Radionics Inc., Burlington, MA, USA). Stereotactic planning computed tomography (CT) scans were performed and co-registered with 1-2 mm slice thickness MRIs. The XKnife™ RT software from Radionics was used for image fusion, contouring and planning. Tumor and organs

at risk delineation was carried out on T1-weighted MRI sequences. A dose of 12 Gy was delivered at the 80% isodose by means of a Varian 2300 LINAC (Varian Medical Systems, Palo Alto, CA, USA).

Symptoms

Pretreatment and posttreatment trigeminal nerve symptoms were defined as subjective or objective decrease in facial sensation or facial pain documented either by patient interview or physical examination. Pretreatment and posttreatment facial nerve symptoms were defined as any decrease in facial nerve function as documented by a decrease in House-Brackmann Grades (H-B Grades I-VI) (12). Guidelines of the AAO-HNS Committee on Hearing and Equilibrium were used to classify patients' preoperative hearing status (13). Cochleovestibular symptoms such as dizziness and tinnitus were also recorded together with the patients' comorbidity and neurological complications.

Quality of life

The median follow-up between treatment and QoL assessment was 34 months (mean, 35 mo; range, 3-78 mo). QoL was measured using the SF-36, which is the most widely used generic questionnaire to assess QoL and has been validated and proven to be a reliable instrument to measure general QoL (14). It consists of 36 items comprising 8 subscales of QoL. These subscales are 1) physical functioning and 2) social functioning, that is, the degree of limitations experienced in daily life physically and socially, respectively; 3) physical role limitations and 4) emotional role limitations, that is, limitations in work or other daily activities due to physical and emotional problems, respectively; 5) mental health, the degree of depression and anxiety; 6) vitality, the degree of energy and exhaustion; 7) bodily pain and 8) general health which quantifies the subjective evaluation of the patient's own health status and pain. Higher scores indicate better perceived QoL. Data on patients' responses were scored according to the instructions on scoring syntax in the SF-36 manual and Dutch population norms are available for reference (15).

Statistical analysis

Statistical analysis was performed using SPSS version 14.0 for Windows. The one sample t-test was used for comparison between SF-36 scores of the radiosurgery patients and the healthy age matched control population. The independent samples

t-test was used for comparison between SF-36 scores of the radiosurgery patients using different patient or tumor variables. A 95% level of significance ($p < 0.05$) was used. Correlations between SF-36 scores and patient- or tumor variables were analyzed using the Pearson correlation coefficient.

Results

Clinical outcome

Tumor control is presented in Table 2. None of the 64 patients required a second treatment at a median follow-up of 31 months. The clinical tumor control rate was therefore 100%. In one patient increase of tumor diameter (2 mm) was observed on the first post-irradiation MRI due to tumor necrosis. A follow-up of more than 3 years showed no further tumor progression in this patient. This resulted in an imaging-defined tumor control rate of 98%.

Table 2. Tumor control after radiosurgery (n = 64).

Tumor arrest (%)	33 (52)
Tumor reduction (%)	30 (47)
Tumor progression (%)	1 (2)
Need for second treatment (%)	0 (0)

The clinical results are presented in Table 3. All 64 patients presented with non-serviceable hearing on the ipsilateral ear before treatment (Class C and D according to the AAO-HNS classification) (13). Dizziness was present in 45 of the 64 patients (70%) before radiosurgery. Tinnitus was initially present in 46 patients (72%). Before radiosurgery, two patients (3%) had H-B Grade II paresis and five patients (8%) experienced facial numbness or facial pain. As expected after treatment all the 64 patients retained non-serviceable hearing (Class C and D according to the AAO-HNS classification). Dizziness worsened in 2 patients (3%), and remained unchanged in 43 patients (67%). The patients who did not report dizziness before treatment (30%) did not develop dizziness after treatment. Tinnitus worsened in 3 patients (5%) and remained unchanged in 43 patients (67%). The patients who did

not report tinnitus before treatment (28%) did not develop tinnitus symptoms after treatment. Two patients (3%) developed facial nerve palsy H-B Grade III at 7 and 8 months after treatment. Facial nerve function did not deteriorate after treatment in the two patients with decreased facial nerve function prior to treatment. Trigeminal symptoms developed in four patients (6%) at 5, 6, 11, and 12 months posttreatment. There was no deterioration of symptoms in the five patients with trigeminal symptoms before treatment. In one patient trigeminal symptoms even resolved at 24 months after treatment.

Table 3. Clinical results after radiosurgery (n = 64).

	Pre-existing deficit (%)	Stable after treatment (%)	Worsened after treatment (%)	New after treatment (%)
Facial nerve	2 (3)	62 (97)	-	2 (3)
Trigeminal nerve	5 (8)	60 (94)*	-	4 (6)
Hydrocephalus	0 (0)	0 (0)	-	1 (2)
New neoplasia	-	-	-	0 (0)
Dizziness	45 (70)	62 (97)	2 (3)	0 (0)
Tinnitus	46 (72)	61 (95)	3 (5)	0 (0)

* in one patient pre-existing trigeminal symptoms improved and disappeared at 24 months after treatment.

One patient (2%) developed hydrocephalus at 4 months after radiosurgery, which was treated with a ventriculo-peritoneal drain and which resolved without permanent sequelae. There were 7 patients who suffered from pre-existing neurologic comorbidity: stroke (n = 5), meningioma (n = 1) and multiple sclerosis (n = 1). One patient was surgically and curatively treated for a small cell lung carcinoma, one patient was curatively irradiated for a prostate carcinoma and one patient was bound to a wheelchair due to orthopaedic problems.

Quality of life

The results of the SF-36 are presented in Table 4. The mean SF-36 scores for the radiosurgically treated patients were lower (i.e., reflecting a poorer QoL) for all subscales except for bodily pain and physical functioning when compared to the mean SF-36 scores of the controls. The SF-36 scores for the dimensions social functioning and general health were statistically significantly lower when compared

to the controls (p = 0.01 and p = 0.001, respectively). The scores for bodily pain and physical functioning did not significantly differ from that of the controls (p = 0.4 and p = 0.9) (Table 4). SF-36 scores did not significantly correlate with tumor size, dizziness, trigeminal or facial nerve function, other sequelae such as hydrocephalus, or comorbidity (all p > 0.05). Physical-role functioning inversely correlated with presence of tinnitus (p = 0.01).

Table 4. SF-36 scores after radiosurgery (n = 64).

Short Form-36 scales	After treatment		Healthy controls	
	Mean	SD	Mean	SD
PF	73.0	27.9	66.7	26.0
SF	74.8*	25.7	83.2	23.7
RF	60.9	44.5	69.1	42.5
RE	76.7	40.4	82.9	33.8
MH	72.5	19.6	75.9	17.3
VT	63.2	25.5	64.2	22.0
BP	77.6	28.4	74.8	28.0
GH	53.6*	11.8	60.1	23.9

SD: standard deviation; * p < 0.05.

Discussion

This study reported on the outcome after radiosurgical treatment for VS from both a QoL and clinical perspective. As many other authors, we demonstrated that a marginal dose of 12 Gy is sufficient to control tumor growth of VS treated with radiosurgery. Our clinical tumor control rate was 100% after a follow-up of 31 months, which corresponded with earlier large series reporting control rates of 97-99% during a follow-up of 3-5.7 years (3-5). In our series, we found favorable facial and trigeminal outcome (97% and 94%, respectively), which is also in line with the results of the abovementioned studies. Hydrocephalus occurred in one patient (2%) at 4 months post-treatment, which was treated with a ventriculo-peritoneal drain and without permanent sequelae. Roche et al. recently reported that newly developed post-

radiosurgery hydrocephalus is generally of low incidence (1%) and that radiosurgery does not decompensate the majority of preexisting radiological hydrocephalus (8).

Dizziness and tinnitus were present in most of our patients before treatment, which was in line with other rates varying between 40-60% and 63-75%, respectively (16). After treatment dizziness and tinnitus worsened in only a fraction of our patients, and there were no patients reporting new dizziness or tinnitus. As reported earlier, dizziness may have serious impact on QoL (10). In this study, however, dizziness did not affect QoL outcomes. Development of tinnitus after VS treatment is generally thought to be unpredictable, but a slight overall increase has been reported. We found a significant inverse correlation between tinnitus and physical daily tasks. This outcome was somewhat surprising, because often patients with tinnitus experience emotional disability instead of physical disability.

We observed that social functioning and general health domains of our treated patients were significantly affected compared to the control sample. For the other 6 QoL domains, no significant difference was observed. Patients with trigeminal symptoms did not have significantly lower pain scores when compared to other patients or the healthy control sample. The 4 patients (2 post-radiosurgery) with H-B Grades II-III did have reduced scores on social and physical functioning domains; however, this observation failed to reach statistical significance.

A possible explanation for the abovementioned results might be that most of the symptoms were already present in most patients even before treatment and that patients adjusted to symptoms over time. This phenomenon is known as response shift (17).

It is now well recognized that microsurgical treatment may have a strong impact on the patients' QoL (18,19). In addition, stability in QoL has been reported following conservative treatment (20,21). We are aware of 5 studies reporting on QoL following radiosurgery (Table 5). Pollock et al. first described functional outcomes after radiosurgery and microsurgery. More recently, they prospectively compared QoL outcomes between these treatment modalities. They concluded that QoL was better after radiosurgery when compared to microsurgery using validated QoL questionnaires (22,23). Van Roijen et al. also investigated QoL for both modalities and emphasized that radiosurgery was more cost-effective than microsurgery (24). A recent study by Régis et al. described more favorable long term outcomes after radiosurgery regarding posttreatment complications and hospital stay using a custom made QoL questionnaire. Furthermore, they also found that most

microsurgically treated patients experienced significantly more psychobehavioral problems such as tiredness, depression and anxiety compared to radiosurgically treated patients. However, there was no significant difference between treatment modalities regarding tinnitus, vertigo or imbalance (25). Myrseth et al. used the SF-36 and found that general QoL, facial nerve function and complications rates were all significantly in favor of radiosurgery when compared to microsurgery. However, QoL of both groups was reduced when compared to the healthy controls. In addition, no clear relationship was found between QoL and facial nerve function, tumor size or cochleo-vestibular symptoms (26). Sandooram et al. recently investigated QoL following radiosurgery, microsurgery and conservative management for vestibular schwannoma using the Glasgow Benefit Inventory (GBI). They found poorer QoL after microsurgery when compared to radiosurgery (27). From these studies it appears that QoL after radiosurgery is generally better when compared to microsurgery. However, when compared to the control populations, impaired QoL still exists for both the treatment modalities.

We acknowledge that the retrospective design is a limitation of the study. By using this kind of approach, it remains unclear whether the QoL outcome is affected by either the radiosurgery or by suffering from the tumor itself. Still, there is evidence to suggest that retrospective measurement of QoL is at least as clinically relevant and scientifically sound as prospective assessment (28). However, when compared to other published results from our center, in which QoL was measured in a sample of untreated VS patients, our radiosurgically treated patients displayed improved QoL (29). From this point of view, it appears that QoL was positively influenced by the radiosurgery and the QoL impairment may probably be caused by suffering from the disease itself. A possible explanation might be that the radiosurgically treated VS patients experienced their illness as being controlled without serious morbidity. In contrast, the untreated patients did not receive treatment yet.

Another limitation of the study might be the use of a generic questionnaire (SF-36) for QoL assessment. It would have been more preferable to combine generic with disease-specific QoL measures. Until now no validated questionnaire is available for assessing VS-specific QoL. This implies that developing a VS-specific QoL questionnaire for this specific category of patients is one research implication of our study.

Table 5. Overview of quality of life results in relation to radiosurgery.

First author	Study design	Sample (n)	Treatment	Questionnaire used for QoL assessment	QoL results
Pollock et al. (23)	prospective	82	RS; MS	HSQ*, DHI	RS significantly better than MS; less dizziness after RS compared to MS; no comparison with healthy sample
Van Roijen et al. (24)	retrospective	145	RS; MS	SF-36	RS better than MS; no comparison with healthy sample; RS more cost-effective than MS; disease-specific symptoms were not evaluated
Régis et al. (25)	prospective	210	RS; MS	Custom made, disease-specific	RS better than MS; no comparison with healthy sample;disease-related symptoms were evaluated
Myrseth et al. (26)	retrospective	189	RS; MS	SF-36	RS significantly better than MS; RS and MS impaired compared to healthy sample;disease-related symptoms were not evaluated
Sandooram et al. (27)	retrospective	165	RS;MS;WS	GBI	RS better than MS; disease-related symptoms were not evaluated
present study	retrospective	64	RS	SF-36	RS impaired when compared to healthy sample; disease-related symptoms were evaluated

QoL: quality of life; Treatment: RS: radiosurgery; MS: microsurgery; WS: wait and scan; Quality of life questionnaires: SF-36: Short Form-36 Health Survey; GBI: Glasgow Benefit Inventory; DHI: Dizziness Handicap Inventory; * short version of the SF-36.

Conclusion

Radiosurgery has become a well-established treatment option for VS. Previous studies have reported long term clinical tumor control rates up to 99% and favorable cranial nerve outcome with low marginal doses. Our study also shows that low dose radiosurgery for VS offered good tumor control and comparable clinical outcome. We found that QoL after treatment was impaired when compared to the age-matched healthy controls, which is also in line with existing literature. There was no significant correlation between the QoL outcome and disease-related symptoms, tumor size or comorbidity.

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Chapter 5

Translabyrinthine surgery for disabling vertigo in vestibular schwannoma patients

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Abstract

Objective: To determine the impact of translabyrinthine surgery on quality of life in vestibular schwannoma patients with rotatory vertigo.

Study design: Prospective study in 18 vestibular schwannoma patients.

Setting: The study was conducted in a multispecialty tertiary care clinic.

Participants: All 18 patients had a unilateral intracanalicular vestibular schwannoma, without serviceable hearing in the affected ear and severely handicapped by attacks of rotatory vertigo and constant dizziness. Despite an initial conservative treatment, extensive vestibular rehabilitation exercises, translabyrinthine surgery was performed because of the disabling character of the vertigo, which considerably continued to affect the patients' quality of life.

Main outcome measures: Preoperative and postoperative quality of life using the SF-36 scores and Dizziness Handicap Inventory (DHI) scores.

Results: A total of 17 patients (94%) completed the questionnaire preoperatively and 3 and 12 months postoperatively. All SF-36 scales of the studied patients scored significantly lower when compared with the healthy Dutch control sample ($p < 0.05$). There was a significant improvement of DHI total scores and SF-36 scales on physical and social functioning, role-physical functioning, role-emotional functioning, mental health and general health at 12 months after surgery when compared with preoperative scores ($p < 0.05$).

Conclusions: Vestibular schwannoma patients with disabling vertigo, experience significant reduced quality of life when compared with a healthy Dutch population. Translabyrinthine tumor removal significantly improved the patients' quality of life. Surgical treatment should be considered in patients with small- or medium-sized tumors and persisting disabling vertigo resulting in a poor quality of life.

Introduction

Vestibular schwannoma (VS) patients usually present with progressive unilateral hearing loss, tinnitus, balance disorder and in some cases vertigo. The incidence of rotatory vertigo in VS has been reported around 10% of cases, and usually the severity and frequency of complaints are diminished because of adequate vestibular compensation (1-4). However, some VS patients continue to experience rotatory vertigo over time.

The unexpected sudden loss of balance or constant illusion of movement, when suffering from rotatory vertigo attacks, may impose a great deal of discomfort on daily life. The vertigo attacks may eventually lead to physical and social limitations and reduce patients' quality of life (QoL). These conditions may reflect on the medical history as perceived by the patient and lead to a discrepancy between the patients' and the clinicians' assessment of the vertigo. When discussing treatment options in cases of VS and vertigo, the clinician has, besides clinical parameters, to rely heavily on the patients' opinion concerning the incidence or severity of the vertigo. As a result of this, QoL plays a key role in choice of treatment for these patients.

In VS literature, most studies focus on vestibular symptoms in general and not specifically on the concommitant vertigo (3,5,6). Several authors have reported on QoL after microsurgery (7-11) or at the degree of vestibular compensation after surgery (12, 13). Vertigo, however, has not been quantified before in VS patients and using validated QoL measures. Furthermore, there are few studies in which vertigo has been discussed as an indication for (surgical) treatment in VS.

Recently, an attempt was made to put 'vestibular symptoms' in VS in a QoL perspective at the Consensus Meeting on Systems for Reporting Results in Acoustic Neuroma in Tokyo, 2001 and results were published by Kanzaki et al. (14). The objective of the meeting was to achieve consensus on a universal reporting system. According to the vestibular symptom grading system (grade I–IV), all patients in this study were classified as grade IV, which is defined as: severe, persistent, or almost persistent dizziness or dysequilibrium incapacitating and severely affecting quality of daily life. All our patients were diagnosed with small non-cystic intracanalicular tumors which were suitable for a wait and scan policy. However, these patients continued to experience rotatory vertigo attacks and intermittent dizziness, despite extensive vestibular rehabilitation exercises during conservative follow-up. Finally, these patients underwent translabyrinthine surgery to primarily achieve tumor

removal and with complete transsection of both vestibular nerves to relieve them from their vertiginious complaints. This study aimed to evaluate the QoL results in these patients and the effect of translabyrinthine surgery on the QoL by using the validated SF-36 and Dizziness Handicap Inventory (DHI) (15,16).

Materials and Methods

Patients

A total of 18 VS patients who had been operated between January 2001 and May 2005 for rotatory vertigo were prospectively studied. Patients were included if they had small non-cystic intracanalicular tumors (with no extrameatal growth) and experienced dysequilibrium with rotatory vertigo or had multiple attacks of vertigo with dizziness during the last year. Our routine neurotologic physical examination included extensive balance testing. They were classified according to the relatively new classification and grading system defined by Kanzaki et al. with grade I: indicating no dizziness or dysequilibrium; grade II: occasional and slight dizziness or dysequilibrium; grade III: moderate or persistent dizziness or dysequilibrium and grade IV: severe, persistent or almost persistent dizziness or dysequilibrium incapacitating and severely affecting quality of daily life (14). All patients were classified as grade IV and had a non-serviceable hearing on the affected ear with an average of 56 dB impairment on pure-tone audiogram (range 30-80 dB). Preoperative balance disorder was also assessed through electronystagmography which showed a poor vestibular compensation for the majority of the patients that could explain the severe impact of their symptoms (n = 15). In three patients preoperative electronystagmography could not be performed because of logistic reasons. After review at our multidisciplinary Skull Base Pathology Meeting for all patients, an initial wait and scanning was decided to await improvement of vertigo. However, during follow-up and despite extensive vestibular rehabilitation exercises no improvement of symptoms occurred and patients underwent translabyrinthine VS excision. There were no postoperative complications in any of the patients. All patients received extensive vestibular rehabilitation exercises preoperatively and postoperatively to stimulate further adaptation of the vestibular systems.

Materials

Patients were asked to complete our QoL questionnaire, which included the validated Dutch version of the SF-36 and a Dutch translation of the validated DHI, preoperatively and 3 and 12 months postoperatively. Medical data were prospectively collected from the patients' medical records.

The Short Form-36 Health Survey

The SF-36 assesses QoL in the following eight domains: physical functioning, social functioning, role-physical functioning, role-emotional functioning, mental health, general health, bodily pain and vitality. For each domain, there is a series of itemised questions that are scored. Each score is coded, summed and presented on a scale of 0-100, where 0 implies the worst possible health status and 100 the best possible. Mean scores were compared with the scores from an age- and sex-matched Dutch healthy sample (n = 1.063), in order to assess the postoperative health status of our patients with matched healthy controls. The questionnaire, which included the SF-36 and DHI, was given to the patients at the pre-admission clinic after the diagnosis of VS was confirmed. They were asked to complete the same questionnaire at both 3 and 12 months after surgery.

The Dizziness Handicap Inventory

The Dizziness Handicap Inventory was developed to assess handicap related to balance problems. It examines the functional, emotional and physical deficits that arise secondary to balance problems and previously used in patients with vertigo (17,18). The scale has shown its reliability and validity. The DHI scores range from 0 (best possible measured health) to 100 (the worst possible).

Statistical methods

The descriptive statistics are presented as mean values with standard deviations. For the analysis of the SF-36, raw scores were calculated for each scale by adding the responses for all items on that dimension; each raw score was then transformed into a 0-100 point scale using the formula described in the SF-36 scoring manual (19). Non-parametric tests were used, because of the non-parametric nature of the data. Comparison of continuous variables was made using the Wilcoxon signed rank test. A 5% level of significance was used. The analysis of DHI scores, used total scores rather than the emotional, physical and functional subscales. This is because, earlier

studies have shown by factor analysis that the original subscale structure of the DHI is of questionable validity (20).

Results

A total of 17 patients (94%) completed the questionnaire preoperatively and 3 and 12 months postoperatively. This group comprised 10 women and seven men with a mean age of 55.9 years at diagnosis (range, 41-69 yr). Seven patients had right sided tumors and 10 patients had left sided tumors, which were all intracanalicular. Average time interval between diagnosis and surgery was 8.4 months. The score distribution of the SF-36 is listed in Table 1. Mean preoperative scores were significantly lower on all eight scales of the SF-36 when compared with the mean scores of the healthy Dutch population sample ($p < 0.05$). There was no significant difference between preoperative scores and 3 months postoperative scores ($p > 0.05$). Scores for physical and social functioning, role-physical functioning, role-emotional functioning, mental health and general health were significantly improved at 12 months postoperatively when compared with preoperative scores ($p < 0.05$). No significant differences were found between preoperative and 12 months postoperative scores for vitality and bodily pain. To illustrate the effects of preoperative vertigo and of translabyrinthine surgery on the SF-36 scales, scores were plotted in relation to the scores of individuals from the Dutch general population (Figure 1). Twelve months after surgery, mean scores were significantly improved compared with the preoperative mean scores, but still reduced when compared with the mean scores of a healthy Dutch sample. The score distribution for the DHI is given in Table 2. Total scores showed no significant difference in preoperative scores, and scores at 3 months after surgery ($p > 0.05$), but significant differences were found between preoperative scores and 12 months postoperatively ($p < 0.05$). Analysis was performed to look at possible drivers for significant change. For an individual's DHI score to have changed significantly, the change has to be at least 18 points (16). Data were recoded and the patients experiencing significant change in DHI scores were included in the analysis and listed in Table 3. When this 18-point criterion is used, DHI scores were significantly improved in 30% of the patients and no significant improvement was observed in 70% of the patients at 3 months post-surgery. There were no significantly worse DHI scores at 3 or 12 months after surgery. At 12 months postoperatively, 88% of patients

had significant improvement in DHI scores when compared with preoperative scores. Hence, for most patients, significant improvement in the QoL and vertigo can be expected only after 3 months postsurgery. Age or sex did not significantly correlate with changes in SF-36 or DHI scores.

Table 1. Mean SF-36 scores of operated patients before and 3 and 12 months after translabyrinthine surgery (n = 17).

Short Form-36 scales	Before		After 3 mo		After 12 mo		Dutch controls	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
PF	61.5	11.0	67.1	15.7	77.1*	12.8	81.9	23.2
SF	65.7	14.3	70.0	9.9	79.4*	17.1	86.9	20.5
RP	54.4	20.2	58.8	23.2	70.6*	20.2	79.4	35.5
RE	60.7	27.0	66.6	28.9	72.5*	29.4	84.1	32.3
MH	60.2	23.7	60.0	15.6	72.9*	19.6	76.8	18.4
VT	57.9	19.8	62.6	12.3	62.1	17.0	67.4	19.9
BP	65.6	25.4	67.9	24.2	69.7	22.7	79.5	25.6
GH	60.0	12.7	60.0	12.8	70.6*	13.7	72.7	22.7

PF, physical functioning; SF, social functioning; RP, role-physical functioning; RE, role-emotional functioning; MH, mental health; VT, vitality; BP, bodily pain; GH, general health; SD, standard deviation; * $p < 0.05$.

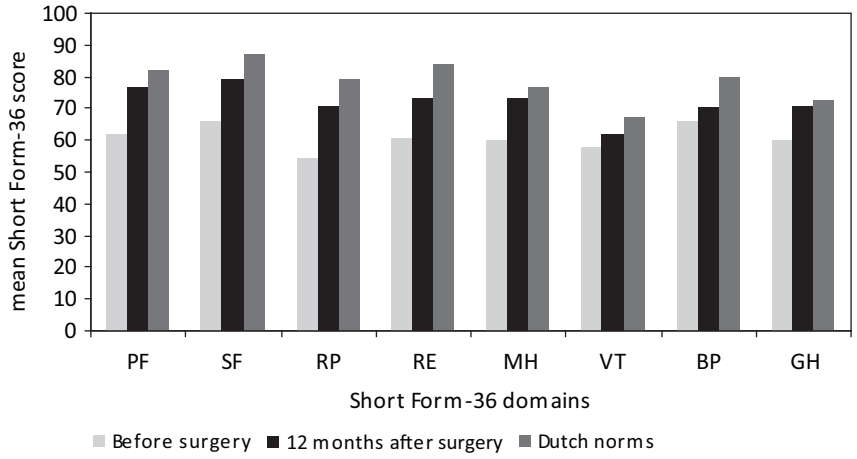

Figure 1. Impact of treatment on scores in VS patients with disabling vertigo.

Table 2. Mean total scores of the DHI of operated patients before and 3 and 12 months after translabyrinthine surgery (n = 17).

DHI total	Mean	Minimum	Maximum	SD
Preoperative	51.3	42	84	13.1
3 months postoperative	38.1	20	52	9.1
12 months postoperative	19.4	12	40	9.5

DHI, Dizziness Handicap Inventory.

Table 3. The number of patients with significant changes in DHI scores.

Change period	Better	No change	Worse
Preoperative to 3 months postoperative	5	12	0
3 months postoperative to 12 months postoperative	8	9	0
Preoperative to 12 months postoperative	15	2	0

Discussion

Our study showed that patients with small tumors but with persistent and disabling vertigo complaints have reduced QoL, which significantly improved after translabyrinthine surgery. It has become clear in personal communication with colleagues from respected centres that, these kind of VS patients are seldomly observed and ultimately most of these patients require surgical intervention. It was also concluded that despite numerous QoL reports in VS literature, no previous study reported on treatment options (i.e., microsurgery, intra-tympanic gentamycin application) when vertigo continues to affect the patients' QoL. There is little evidence concerning the effects of intra-tympanic gentamycin on vertigo in VS patients. A (chemical) labyrinthectomy using intra-tympanic gentamycin is mainly performed in patients with Meniere's disease and high success rates are reported. Brantberg et al. proposed gentamycin as a treatment in vestibular diseases other than Meniere's disease, however, only one VS patient in their series was treated with intra-tympanic gentamycin. They concluded that the intra-tympanic instillation with gentamycin may further increase symptoms as hearing loss and tinnitus in these patients. Moreover,

the underlying mechanism of vertigo attacks in vestibular schwannomas is still not completely understood (21).

Generally, patients with small-sized tumors are recommended a wait and scan policy, especially when symptoms are mild and QoL is not severely affected. All of our patients had small-sized tumors, but experienced rotatory vertigo grade IV (according to the classification proposed by Kanzaki et al. (14)), despite extensive rehabilitative therapy during follow-up. To relieve them from their vertigo and to achieve tumor removal, translabyrinthine surgery was finally undertaken. Transsection of both the vestibular nerves and/or tumorexcision resulted in stability of incoming signals in the vestibular nuclei. Immediately after VS surgery, patients experienced vestibular crisis, but this acute stage was followed within days or weeks with gradual improvement of symptoms due to proper compensation and adaptation of the vestibular nuclei. Most of our patients, experienced these symptoms only for a few weeks or months postoperatively, but instability of balance has been reported after surgery (3,5,22,23). Two patients continued to experience instability of balance even after 12 months post-surgery and reported no significant change in DHI scores (Table 3). This relative imbalance is induced by the ablation of the vestibular function in the operated ear. Every patient must be informed about this sequelae before surgery, especially in whom the surgery is performed to control the vertigo. The DHI total scores showed significant improvement after surgery in 88% of our patients at 12 months after surgery, resulting in a postoperative score of 19.4 points. When compared with other reported DHI scores of patients with general vestibular dysfunction or Meniere's disease, our patients scored significantly better (24,25). Comparison of DHI scores with a general VS population after surgery or with benign paroxysmal positional vertigo patients showed no large differences (Table 4) (5,6). SF-36 results showed that the QoL in VS patients suffering from vertigo was significantly reduced on all eight scales when compared with Dutch healthy sample. Postoperatively, scores were significantly improved for almost all of the SF-36 scales when compared with preoperative scores. However, SF-36 results were still lower in patients than that of the healthy control sample, which is in agreement with the results of previous studies (8, 9,10). To our knowledge, there is no previous evidence which reported on the QoL or any (surgical) intervention in a comparable patient sample. This may be due to the fact that the treatment of VS has focused on tumor excision or preservation of cranial nerve function instead of relieving symptoms reported by patients.

Table 4. DHI scores as reported by other investigators.

First author	Mean age (yr)	Population	Mean scores
Humphriss et al. (6)	56	after vestibular schwannoma surgery	21.0
El Kashlan et al. (5)	53	after vestibular schwannoma surgery	17.0
Kinney et al. (24)	50	Meniere's disease	41.0
Enloe et al. (25)	56	general vestibular dysfunction	53.6
Lopez et al. (17)	50	posterior canal benign paroxysmal positional vertigo	18.1
present study	56	after vestibular schwannoma surgery	19.4

Comparison with other studies

Recently, a prospective study was performed by Myrseth et al. (26) who tried to identify a relationship between cochleovestibular symptoms and QoL in VS by using the SF-36 and visual analogue scales. They found that vertigo strongly affects the QoL and suggested that this symptom should play a key role in discussing treatment options in small- and medium-sized vestibular schwannomas. However, they concluded that more clinical evidence is needed to confirm this hypothesis. The results of our study seem to contribute to this hypothesis, but the relatively small sample size of the study should be taken into consideration when interpreting the study results. Most of our patients reported major differences between preoperative and postoperative QoL and SF-36 and DHI scores were statistically significant. The study was conducted in a prospective manner and by using validated and widely used generic and disease-specific questionnaires. In addition, the SF-36 and the DHI have been previously used in studies reporting on efficacy of treatment of vestibular dysfunction. Enloe et al. (25) described a general correlation between the two scales before and after vestibular rehabilitation intervention and recommended using the two scales together for optimal QoL assessment in patients with vestibular disorders.

Conclusions

QoL in VS patients with disabling vertigo symptoms has not yet been investigated. It concerns a small cohort of patients within our VS population with vertigo symptoms that are classified as grade IV according to the classification of Kanzaki et al. (14). This study found that the QoL is reduced in these patients despite rehabilitation exercises to control the vertigo. Finally, translabyrinthine surgery was performed and postoperative results show that at 12 months after surgery, QoL and vertigo were significantly improved for most patients. Until now, evidence for other possible treatment options in these patients is limited. These findings suggest that surgical treatment should be considered in patients with small- or medium-sized tumors and persistent disabling vertigo resulting in poor QoL.

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Chapter 6

Intratemporal facial nerve transfer with direct coaptation to the hypoglossal nerve

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Abstract

Objective: To evaluate functional recovery after facial-hypoglossal nerve transfer with direct coaptation of the intratemporal part of the facial nerve.

Study Design: Retrospective study.

Setting: University-based tertiary referral center.

Patients: Nine patients who underwent facial-hypoglossal transfer surgery between 2001 and 2006 to treat unilateral complete facial nerve palsy.

Intervention: The facial nerve is mobilized in the temporal bone, transsected at the second genu, transferred and directly coaptated to a partially incised hypoglossal nerve.

Main Outcome Measures: The House-Brackmann grading system was used to evaluate facial nerve reinnervation. Tongue atrophy and movements were documented. Quality of life related to facial function was assessed using the validated Facial Disability Index.

Results: A House-Brackmann Grade III (86%) was achieved in six patients, and Grade IV (14%) in one patient with an average follow-up of 22 months (range, 12-48 mo). Two patients had a follow-up of less than 12 months after surgery, and reinnervation was still in progress. In none of the patients who were operated on was tongue atrophy or impaired movement observed. Postoperative Facial Disability Index scores (mean, 71.8 ± (SD) 10.6) for physical functioning and social functioning (mean, 85.7 ± 9.8) were increased for all patients when compared with preoperative scores (mean, 28.6 ± 9.0; mean, 37.7 ± 14.4, respectively).

Conclusion: The facial-hypoglossal nerve transfer with direct coaptation of the intratemporal part of the facial nerve offers good functional results with low lingual morbidity and improved quality of life. The technique is straightforward, relatively simple, and should be considered as first option for reanimation of traumatic facial nerve lesions.

Introduction

Traumatic facial nerve lesions may potentially cause lifelong functional, cosmetic, and emotional problems (1,2). When facial nerve continuity is lost, preferably, immediate nerve repair through primary neurorrhaphy with direct coaptation or grafting should be attempted. When continuity is intact, but spontaneous recovery does not occur, delayed repair through hypoglossal-facial nerve transfer is a treatment option. The classic hypoglossal-facial end-to-end nerve transfer (classic HFT) has long been advocated as the primary choice (3,4). In this technique, the hypoglossal nerve is completely transected and transferred to the facial nerve, which is transected at the stylomastoid foramen level, to obtain direct coaptation. Classic HFT inevitably results in hemiglossal paralysis and hemitongue atrophy, which in turn affects speech, mastication, and swallowing in 45% to 59% (5,6). Additional disadvantage of the classic HFT is hypertonia, spasm, and synkinesis in the facial musculature due to massive reinnervation (5).

In an effort to reduce the adverse effects of HFT, a number of technical modifications have been applied (Table 1). For instance, only a part of the hypoglossal nerve is transsected and transferred by longitudinally splitting (split HFT) (7,8). Functional results of facial reanimation are good (100% House-Brackmann Grade III), but all patients experienced some degree of hemiglossal atrophy. Another modification of the HFT was introduced by May et al. (9) using a “jump” interposition graft between a partially incised hypoglossal nerve and the facial nerve. Results showed preservation of tongue function in 87% of patients. However, a longer recovery time was observed, and facial muscle reanimation is less than after the classic technique. The latter is likely caused by the use of a graft, which causes loss of regenerating axons at two coaptation sides. In addition, morbidity related to harvesting of a nerve graft has been reported (10). To avoid the use of a graft, Atlas and Lowinger (11) described the transfer of the intratemporal facial nerve to gain facial nerve length and obtain a direct coaptation to the hypoglossal nerve. Since the initial report of this technique, few studies have reported about the outcome of this technique, and only small patient cohorts are described (12-15). Results of facial function are claimed to be as good as those in patients who underwent classic HFT, however, without additional deficits. The purpose of this study was to present this relatively new modification and evaluate surgical outcome.

Table 1. Overview of hypoglossal-facial nerve modifications.

First author	Coaptation technique	N	Interval from FP to RFS (mo)	H-B grade in %					Tongue atrophy (n)		
				II	III	IV	V	VI	M	MO	S
Conley and Baker (3)	classic	137	2-55		65	18	17		1	70	37
Magliulo et al. (19)	classic	10	1-23		40	50	10		2	5	3
Kunihiro et al. (20)	classic	42	3 - 33	2	38	52	7		27	7	8
May et al. (9)	graft	20	0 - 48		80	15	5		21	1	0
Manni et al. (21)	graft	29	4 - > 24	21	45	24	7	3	0	0	0
Arai et al. (8)	split	8	1 - 6		100				3	5	0
Atlas and Lowinger (11)	direct	3	2-6			100			0	0	0
Donzelli et al. (14)	direct	3	12-14		33	67			3	0	0
Sawamura and Abe (12)	direct	4	20-37		75	25			0	0	0
Darrouzet et al. (13)	direct	6	0-110		83	17			2	0	0
Rebol et al. (15)	direct	5	8-13		40	20	20	20	0	0	0

FP, facial paralysis; RFS, rehabilitative facial surgery; H-B, House-Brackmann; M, minimal; MO, moderate; S, severe; classic, end-to-end HFT; graft, hypoglossal-facial nerve interposition jump graft; split, HFT with a split hypoglossal nerve; direct, FHT with direct coaptation of the intratemporal facial nerve.

Materials and Methods

Patients

A total of nine patients underwent facial-hypoglossal nerve transfer with direct coaptation (FHT) between August 2001 and May 2006 and were retrospectively examined. These patients presented with a unilateral complete facial nerve paralysis after surgery for vestibular schwannoma (n = 5), cerebellar pilocytic astrocytoma (n = 1), cholesteatoma (n = 1), and facial nerve schwannoma (n = 1). One patient had progressive facial paralysis (H-B Grade V) due to progression of a jugulotympanic glomus tumor. The average time interval between facial paralysis and reconstructive surgery was 7.8 months (range, 0-15 mo). Facial nerve function was recorded at a minimum of 12 months after surgery and using the House-Brackmann (H-B Grades I-VI) classification (16). Tongue atrophy was photographically documented and separately quantified by two observers (one of the senior authors and the first author) as severe, moderate, low, or absent. Tongue movements were scored as

normal of abnormal. Patients reported both their preoperative and postoperative facial function using the Dutch translated version of the Facial Disability Index (FDI) questionnaire at the end stage of reinnervation. The FDI is a disease-specific, selfreport instrument for the assessment of disabilities of patients with facial nerve disorders as perceived from the patients' perspective. It consists of 10 questions that indicate the level of social handicap (FDI-social) and physical disability (FDI-physical) from facial nerve dysfunction. Both indices use a 100-point scale with higher scores indicating less handicap or less disability (17,18).

Surgical technique

A lazy S-shaped parotid incision was made toward the mastoid tip and then extended along the anterior edge of the sternocleidomastoid muscle to the hyoid bone. Identification of the extratemporal part of the facial nerve was performed using the tragal pointer and posterior belly of the digastric muscle. The facial nerve was mobilized in its distal part as far as the trifurcation in the parotid gland. The sternocleidomastoid muscle was retracted posteriorly for maximal exposure of the mastoid process, and the proximal portion of the facial nerve was dissected free up to the stylomastoid foramen (Figure 1A). The mastoid was drilled until the facial nerve was exposed from the level of the stylomastoid foramen to the external facial nerve genu, transected at the external genu and transferred (Figure 1B). In this way, additional facial nerve length of 1.5 to 2 cm was obtained, allowing for a tensionless coaptation to the hypoglossal nerve. The hypoglossal nerve was found at the level of the carotid bifurcation and dissected as proximally as possible. A tailor-made partial transsection of the hypoglossal nerve was subsequently performed at the site where the transferred distal facial nerve would be coapted, which was equal to the cross-sectional diameter of the facial nerve. Usually this was less than half of the hypoglossal nerve diameter. A tensionless coaptation between the two nerve endings, the proximal "hemi"-transected hypoglossal nerve and the distal part of the facial nerve, was made (Figure 1C). The epineurium and perineurium of the two endings were sutured using three Ethilon (Ethicon, Amersfoort, The Netherlands) 10.0 nylon sutures and Tissuecol (Immuno AG, Vienna, Austria) fibrin glue was applied.

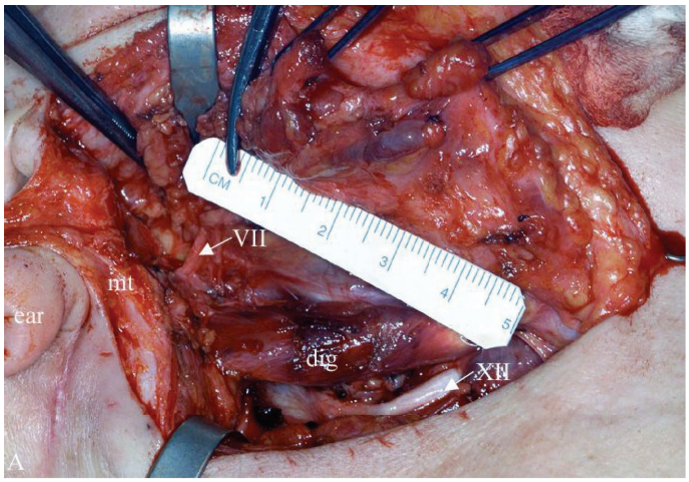

Figure 1. Intraoperative photographs of FHT. A: The 7th (VII) and 12th (XII) nerves are dissected, respectively (mt: mastoid tip; dig: digastric muscle).

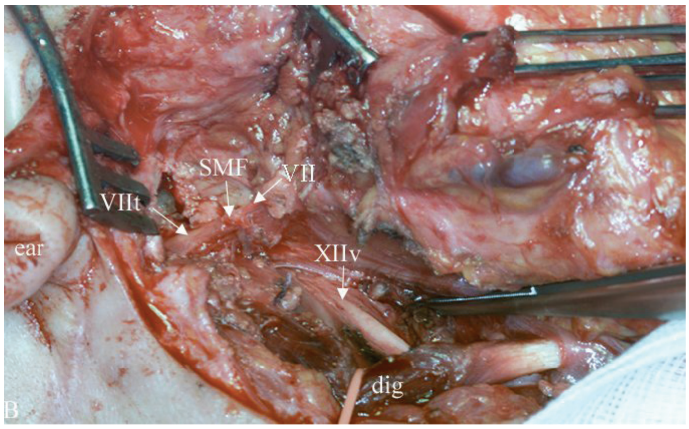

Figure 1. B: The stylomastoid foramen (SMF) is dissected and the intratemporal part (VIIt) of the 7th nerve is exposed after drilling the mastoid tip (XIIv: vertical part of the 12th nerve).

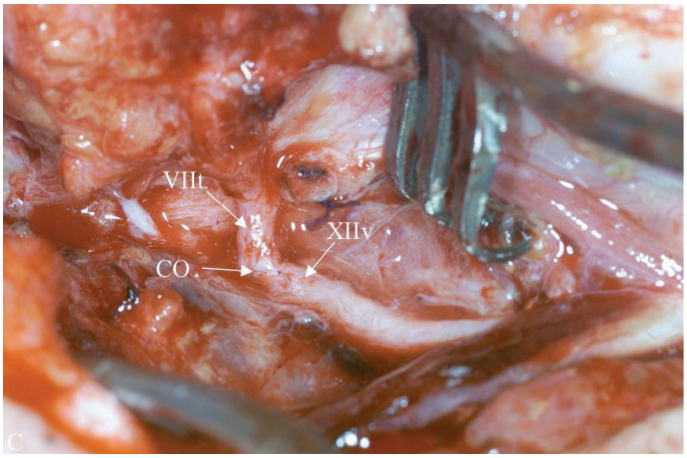

Figure 1. C: The intratemporal 7th nerve is transferred (VIIt) to the vertical part of the 12th nerve (XIIv) in an end-to-side coaptation (CO).

Results

The study comprised 7 female and 2 male patients with mean age of 35.4 years (range, 9-61 yr). The patients' facial muscle tonus showed first signs of recovery at 6 months postoperatively and with movements recorded around the mouth. In 2 patients, follow-up was less than 6 months, and this is too short a period for the reinnervation process. Results of facial nerve function in the remaining 7 patients showed H-B Grade III (86%) in 6 patients and H-B Grade IV (14%) in 1 at an average follow-up of 22 months after surgery (range, 12-48 mo) (Table 2; Figures 2A, B). The follow-up time in the patient with H-B Grade IV was relatively short (13 mo). Tongue atrophy was absent in all patients, and tongue function was normal (Figure 2C). Preoperative and postoperative FDI subscores are provided in Table 3. There was a significant difference between preoperative and postoperative FDI-physical and FDI-social subscores (Wilcoxon signed rank test, $p < 0.05$). Average FDI physical scores were 28.6 points (SD ± 9.0) preoperatively and 71.8 points (SD ± 10.6) postoperatively. Average FDI social scores were preoperatively 37.7 points (SD ± 14.4) and 85.7 points (SD ± 9.8) postoperatively. All 7 patients reported improved FDI scores on both sub-scales. There were no surgical complications in the patients who were operated on.

Table 2. Results and characteristics of the patients who were operated on.

Patient no.	Age (yr)	Sex	Cause of facial paralysis	Preoperative (H-B)	Postoperative (H-B)	Interval lesion -surgery (mo)	Follow-up (mo)
1.	28	M	vestibular schwannoma	VI	III	5	12
2.	54	F	astrocytoma	VI	III	12	17
3.	19	F	vestibular schwannoma	VI	III	15	48
4.	16	F	glomus tumor	V	III	7	12
5.	61	F	vestibular schwannoma	VI	III	3	32
6.	52	F	vestibular schwannoma	VI	III	3	20
7.	38	F	vestibular schwannoma	VI	*	11	3
8.	9	M	cholesteatoma	VI	IV	14	13
9.	38	F	facial nerve schwannoma	VI	*		6

H-B, House-Brackmann; M, male; F, female; * : incomplete follow up, no grading performed.

Figure 2. Case 6. Postoperative outcome 12 months after this patient underwent FHT on the right side. A: Patients' face at rest.

Figure 2. B: Patient closing both eyes.

Figure 2. C: Patient closing her right eye firmly by using her tongue and no tongue atrophy or lingual hemiparesis is observed.

Table 3. Mean preoperative and postoperative FDI scores.

FDI	Preoperative	SD	Postoperative	SD
FDI-physical	28.6	9.0	71.8 *	10.6
FDI-social	37.7	14.4	85.7 *	9.8

FDI indicates Facial Disability Index; * p< 0.05; SD, standard deviation.

Discussion

The hypoglossal nerve can be used for dynamic rehabilitation of facial nerve function. Indications are when the proximal stump of the facial nerve is unavailable or when after neurootologic surgery, an anatomically intact facial nerve, does not recover in time. Several modifications to the classic HFT have been proposed to improve facial function and minimize tongue function deficits (7-9). In this study, we have used a relatively new technique in which 1.5 to 2 cm of facial nerve is freed from its canal in the mastoid bone to perform a direct coaptation to a restricted part of the hypoglossal nerve. Using this technique, in 86% of our patients, we achieved the main goals of rehabilitative facial surgery: functional oral sphincter musculature and sufficient eye closure to prevent any eye problems. In addition, tongue function was preserved in all patients, and no tongue atrophy was observed. Our results confirm those of FHT published by other authors (11-13). The FHT is a relatively straightforward and easy technique as compared with modifications with the application of nerve grafts. It is also a safer procedure because there is only one nerve coaptation site. This factor reduces the potential risk of failure of the reconstructive procedure caused by dehiscence.

After facial nerve rehabilitation, patients experience some mass movement and often a nonfunctional frontal muscle. In practice, functional recovery is rarely better than H-B Grade III. The House-Brackmann grading system is widely used by surgeons to grade facial nerve function and rate their surgical success, but it does not reflect the patients' perception of their surgical results. Therefore, we also evaluated outcome using a quality of life (QoL) assessment related to facial nerve function (17). In this study, significantly higher FDI scores on physical functioning and social functioning were found after surgery as compared with preoperative FDI scores. Patients reported functional improvement while eating, drinking, or closing the eye,

and less social limitations related to their facial function. However, one should be cautious while interpreting QoL test results. The patient sample is small, and the preoperative facial function FDI was scored at the same time as the postoperative FDI score and therefore may be biased. Functional nerve recovery is inversely related to the interval between nerve lesion and nerve repair (22, 23). The timing of hypoglossal nerve transfer is difficult, especially after removal of tumor in the cerebellopontine angle when facial nerve continuity is anatomically spared, but postoperative facial muscle reinnervation does not take place. In such instance, we currently perform electromyography examination of the facial musculature at 6 months. If there are no signs of reinnervation in any of the three facial nerve branches, facial-hypoglossal nerve transfer is performed soon after.

Conclusion

The facial-hypoglossal nerve transfer with direct coaptation of the intratemporal part of the facial nerve offers comparable facial nerve function results without lingual morbidity. The FHT is relatively simple and straightforward and is now our first option. Our results are comparable to those of alternative techniques.

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Chapter 7

Surgery for large vestibular schwannoma: residual tumor and outcome

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Abstract

Objective: To evaluate clinical outcome with regard to the amount of residual tumor after surgery for large vestibular schwannoma.

Patients: Between the period of January 2000 and December 2005 a total of 51 large vestibular schwannoma tumors with extrameatal diameter of 2.6 cm or greater (mean 32 mm; median 30 mm; range 26-50 mm) were operated using the translabyrinthine approach. The extent of the resection was intraoperatively estimated as complete, near and subtotal. The amount of residual tumor was measured and the shape and localization was scored on gadolinium-enhanced MR imaging. Correlation between intraoperative and MRI assessment was performed using the Fisher's exact test. Potential growth of residual tumor was documented with frequent MRI follow-up. Postoperative facial nerve function was classified according to the House-Brackmann classification.

Results: Complete resection was performed in 26% of the patients, near-total resection in 58% and subtotal resection in 16%. MRI showed residual tumor in 46% of patients (mean, 16.7 mm; SD, ± 8, range, 5-36 mm). Postoperative facial nerve function was House-Brackmann Grades I-II in 78% of the patients. The intraoperative assessment of near-total resection did not correlate with postoperative MRI ($p = 0.25$). Postoperative MRI showed either no residual tumor or residue that should actually have been classified as a subtotal resection. After a follow-up of 4 years (49 mo; mean, 48 mo), 94% of patients did not show changes on MRI.

Conclusions: Tumor control with good facial nerve function could be obtained in most patients. Intraoperative assessment did not correlate with the amount of residual tumor on postoperative MRI. Objective documentation with postoperative MRI to measure the extent of removal is therefore mandatory.

Introduction

The outcome of vestibular schwannoma (VS) surgery is mainly determined by the extent of tumor removal and preservation of neurological function. Complete tumor removal carries an increased risk of facial nerve paresis, especially in large tumors (1,2). To preserve facial nerve function and maintain quality of life (QoL), the surgeon may leave some tumor in situ. The completeness of tumor removal in surgical literature is usually reported in three groups: complete, near or subtotal. Near-total (or partial) resection is defined as a residue of less than 5% of the original tumor size and subtotal resection as more than 5% (3). Objective assessment of the actual extent of removal documented with postoperative gadolinium-enhanced magnetic resonance imaging (MRI) scans, however, is scarcely provided (4-10). Intraoperative assessment of the extent of tumor removal lacks objectivity. The lack of objective postoperative MRI data on tumor resection has consequences for interpreting the total outcome of surgical treatment. For instance, postoperative facial nerve function should be significantly better when tumor is deliberately left behind.

In 2001 the consensus meeting on VS in Tokyo proposed a system for reporting surgical results in VS (3). Regarding the amount of residual tumor, it was stated that the extent of tumor removal should be confirmed on postoperative gadolinium-enhanced MRI scans. The size of the residue should be described in two perpendicular diameters and with its subsequent localization: within the meatus, outside the meatus along the cranial nerves and at the brainstem or the cerebellum.

In the present study we report on the surgical results after translabyrinthine surgery for large vestibular schwannomas (≥ 2.6 cm) focused on residual tumor. The amount of residual tumor as (intraoperatively) estimated by the surgeon and the amount of residual tumor as documented on postoperative MRI scans were compared. When residual tumor was present, the location and size was further classified according to Kanzaki et al. (3). Moreover, correlation between facial nerve function and presence or absence of residual tumor and regrowth in time was studied.

Materials and Methods

Patients

Between the period of January 2000 and December 2005, a total of 51 VS tumors with extrameatal diameter of 2.6 cm or greater were operated using the translabyrinthine approach. Patients with NF2 or incomplete follow-up were excluded from the analysis. One patient was lost to follow-up which resulted in 50 patients (17 men and 33 women) who were retrospectively studied. The mean age of the patients was 49 ± 14 years (range, 19-75 yr). The completeness of removal was peroperatively estimated as complete; near-total or partial removal, in which less than 5% of the initial tumor was left in situ, and subtotal removal, in which more than 5% of the initial tumor was left in situ (3).

Preoperative and postoperative facial nerve function was classified according to the House-Brackmann (H-B) classification (11). Guidelines of the AAO-HNS Committee on Hearing and Equilibrium were used to classify preoperative hearing status (12). All 50 patients preoperatively had non-serviceable hearing on the tumor ear (Classes C and D according to the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)).

Preoperative tumor size

Preoperative tumor size was defined using the largest extrameatal diameter on an axial 1.5 T MRI T1-image with gadolinium enhancement (Magnevist®, Bayer, Utrecht, The Netherlands). The following group classification was used: intrameatal tumors, small tumors (1-10 mm), medium (11-25 mm), large (26-40 mm) and extra large (> 40 mm) (13). The mean tumor size was 32 mm ± 6.0 mm (range, 26-50 mm). There were 45 patients (90%) with large tumors and 5 patients with extra large tumors (10 %).

Residual tumor

The amount of residual tumor was evaluated on postoperative 1.5 T MRI (Gyroscan®, Philips Medical Systems, Eindhoven, The Netherlands) scans using axial T1-weighted sequences with a slice thickness of 1 millimeter, with gadolinium enhancement, and fat suppression. According to our standard postoperative protocol, a “baseline” MRI was performed in all patients at a mean of 11 months ± 7 months (range, 2-39 mo) after surgery. This protocol requires a first MRI scan between 6 and 12 months after surgery. Of the 50 patients, 46 (92%) were scanned within this required interval.

During our follow-up program, a second scan (mean 29 ± 9 mo postsurgery; range, 15-51 mo) and a third scan (mean, 49 ± 17 mo postsurgery; range, 28-94 mo) were performed to observe possible changes in enhancement or growth of residue. All MRI data were evaluated by the first author and the neuroradiologist (FB) blinded for the intraoperative assessment data of the surgeons. The largest diameter of the entire enhancement (in millimeters) in any of the axial 1-mm T1-images was measured on the baseline postoperative MRI scan. The surface (in square millimeters) of the preoperative tumor and postoperative residual tumor was also measured on axial MRI scans.

When interpreting MRI scans after VS surgery, it is now recognized that slight linear high-signal enhancement in the internal auditory canal (IAC) corresponds to dura mater inflammation or postoperative scar tissue, whereas nodular enhancement in the IAC or cerebello-pontine angle (CPA) is suspected for recurrent or residual tumor (14,15). Therefore, the enhancement in the IAC and CPA was analyzed for a linear and / or nodular aspect or pattern. Enhancement pattern corresponding with dura mater inflammation or scar tissue were not classified as residual tumor. The exact location of the enhancement was then assessed according to the Kanzaki classification of residual tumor: residual tumor within the meatus, outside the meatus along the nerves, or at the brainstem or cerebellum (3). The location of the largest part ("bulk") of the enhancement was used and classified according to the classification of Kanzaki. The differences within groups and between groups were calculated using the Student's t-test, Chi square test, and the Fisher's exact test was used to assess correlations. Statistical significance was set at $p < 0.05$ (SPSS software version 14.0 for Windows).

Results

The surgical team intraoperatively estimated that in 13 (26%) of 50 cases a complete removal was performed and that in 37 patients (74%), tumor was left in situ. Of these 37, in 29 (58%) patients, a near-total removal was achieved, whereas in 8 (16%) patients a subtotal removal was performed. Regarding the mean preoperative tumor size, there was no significant difference between complete, near and subtotal groups (resp. 31, 31 and 34 mm; $p = 0.3$).

In 27 (54%) patients of the 50 patients, enhancement was observed on the first postoperative gadolinium-enhanced T1-weighted MR images (mean, 11 ± 7 months; range, 2-39 months). For these 27 patients, the mean diameter of the enhancement observed on MRI measured 15.7 mm (SD, ± 8; range, 5-36 mm). Of these 27 patients, 14 patients had an enhancement with a linear-nodular configuration, and in 9 patients, an enhancement with a single nodular configuration was observed. In 4 patients, the enhancement had a slight linear configuration (Figure 1A).

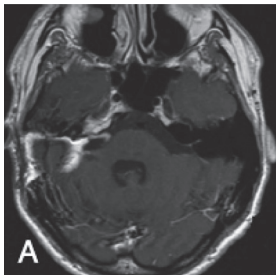

Figure 1A. Postoperative contrast-enhanced T1 MRI axial scan showing linear enhancement in the IAC.

Of the 14 patients with a linear-nodular configuration, the largest part of the enhancement was located near the brainstem (according to the classification of Kanzaki). Of the 9 patients with a single nodular configuration, the largest part of the enhancement on MRI was observed just outside the meatus along the facial nerve. In 4 patients with a slight linear configuration, the enhancement was localized in the IAC. In these patients the enhancement was not classified as residual tumor. A second and third MRI follow-up scan showed an unchanged linear configuration for these patients.

As a result, 23 patients (46%) of the 50 cases had MRI findings corresponding with residual tumor (mean, 16.7 mm; SD, ± 8, range 5-36 mm).

All of these 23 patients were intraoperatively classified as either a near-total or subtotal removal. There was no residual tumor observed in patients intraoperatively classified as complete removal (Table 1). Correlations between the intraoperative estimation and the postoperative MRI results showed that when the surgeon estimated the removal as either complete or incomplete (near- or subtotal), this observation significantly correlated with the MRI results ($p = 0.01$). The intraoperative

assessment of the surgeon regarding the presence of residual tumor may therefore be considered as reliable.

Table 1. Postoperative MRI assessment of the completeness of tumor removal.

MRI	Intraoperative assessment			
	Complete	**Near-total**	**Subtotal**	
Residu	0	15	8	23
No residu	13	14	0	27
Total	13	29	8	50

The group that was surgically qualified as a near-total resection (n = 29) had residual tumor on MRI in 15 patients (mean, 14.6 mm; SD, ± 7.5; range, 5-34 mm), whereas in 14 patients no residual tumor was observed. In all 8 subtotally operated patients, residual tumor was present on MRI (20.75 mm; SD, ± 7.7; range, 10-36 mm). The mean diameter of the residual tumor on MRI between the group classified as near-total and the group classified as subtotal was not significantly different (p = 0.2; Figure 1B).

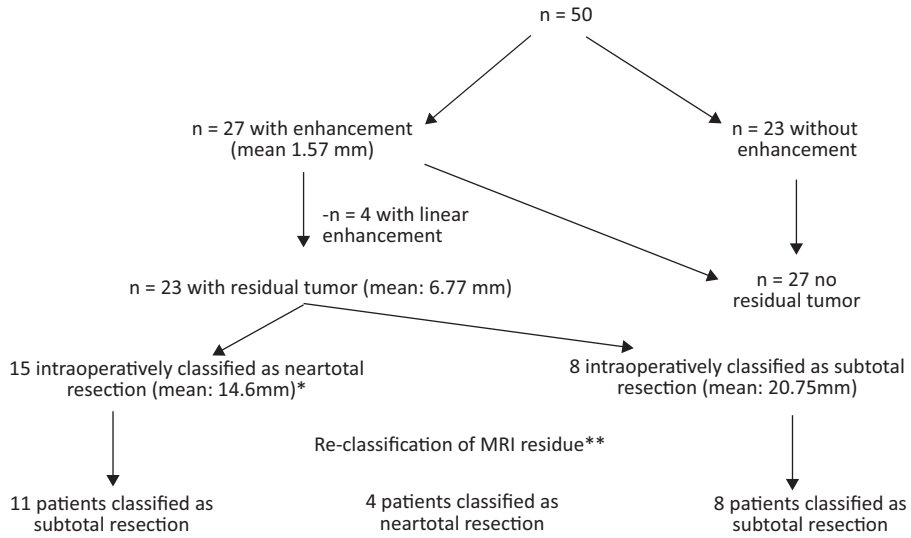

Figure 1B. Flow chart demonstrating the intraoperative and postoperative MRI reclassification of the amount of residual tumor (*p = 0.2, no significant difference in tumor size between groups) (**according to the 5% definition: postoperative tumor size (mm^2) / preoperative tumor size (mm^2) x 100%).

A near-total removal (or partial removal) is defined by tumor resection, of which less than 5% of the initial tumor is left in situ. A subtotal removal is defined by tumor resection, of which more than 5% of the initial tumor is left in situ (3). Of the 23 patients with residual tumor on MRI, the surface area (in square millimeters) of the residual tumor was compared to the preoperative surface area of the initial tumor. If the amount of residual tumor on MRI was less than 5% of the initial tumor size, then the residual tumor was reclassified as near-total resection. If the amount of residual tumor on MRI was more than 5% of the initial tumor, the residual tumor was reclassified as subtotal resection (Figure 1B). The MRI results show that of the 15 tumors that were intraoperatively estimated as a near-total resection, 11 tumors were in fact subtotal resections according to the 5% definition. Only 4 tumors that were intraoperatively assessed as a near-total resection were actually classified as near-total resection on the postoperative MRI (according to the 5% definition; Table 2; Figure 1C and D). All of the 8 tumors that were intraoperatively estimated as a subtotal resection were classified as subtotal resection on postoperative MRI (according to the 5% definition; Table 2; Figure 1E and F). The intraoperative assessment regarding near-total resection did not correlate significantly with postoperative MRI results ($p = 0.25$). The estimation of the surgeon regarding a near-total removal can therefore not be considered as reliable.

Table 2. MRI classification of residual tumor for the near- and subtotal (sub)groups.

MRI measured residu	**Intraoperative assessment**		
	Near-total	**Subtotal**	**Total**
Near-total	4*	0	4
Subtotal	11*	8	19
Total	15	8	23

* $p = 0.25$.

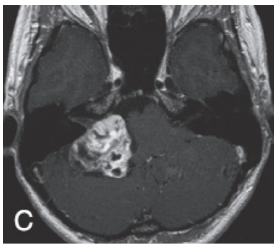

Figure 1C. Preoperative contrast-enhanced T1-weighted MRI axial scan showing a tumor with a diameter of 43 x 30 mm.

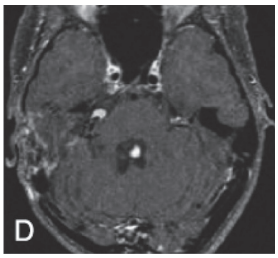

Figure 1D. Postoperative contrast-enhanced T1-weighted MRI axial scan showing residual tumor with a diameter of 10 x 6 mm. The resection was classified as near-total both intraoperatively and after reclassification on MRI.

Facial nerve outcome

Facial nerve outcome in relation to completeness of removal is presented in Table 3. In 39 patients (78%), H-B Grades I to II were achieved at an average of 12 months (SD, ± 4 mo) (range, 2-24 mo) postoperatively. In 11 patients (22%), there were H-B Grades III to IV. In 2 of these patients, the facial nerve was anatomically not intact, and facial nerve reconstruction was performed. In 1 patient, a sural nerve graft was directly interposed, and in the other a (delayed) facial-hypoglossal nerve transfer with direct coaptation of the intratemporal part of the facial nerve was performed (16). Finally, in both patients, H-B Grade III was achieved. There were no patients with H-B Grades V to VI.

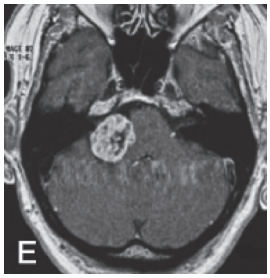

Figure 1E. Preoperative contrast-enhanced T1-weighted MRI axial scan showing a tumor with a diameter of 28 x 20 mm.

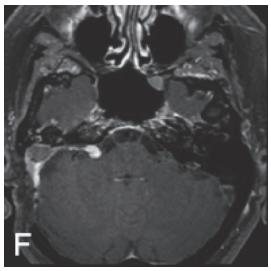

Figure 1F. Postoperative contrast-enhanced T1-weighted MRI axial scan showing a residual tumor with a diameter of 15 x 8 mm. The resection was classified as subtotal both intraoperatively and after reclassification on MRI.

In the near-total and subtotal operated group, a relatively high number of patients have a favorable facial nerve outcome (H-B Grades I-II) when compared with patients with complete resections, although this difference was not statistically significant ($p = 0.4$; Table 3). In our series, facial nerve outcome did not correlate significantly to tumor size ($p = 0.6$).

Table 3. Facial nerve outcome according to completeness of removal (n = 50).

	Complete	Near-total	Subtotal	
Grades I-II	9*	22*	8*	39
Grades III-IV	4	7	0	11
Grades V-VI	0	0	0	0
Total	13	29	8	50

* p = 0.4.

In Table 4, facial nerve outcome is presented in relation to residual tumor on MRI. Facial nerve function H-B Grades I to II was equally distributed in the residual tumor group as in the group without residual tumor on MRI. An unfavorable facial nerve outcome (H-B Grades III-IV) was mainly found in patients without residual disease (n = 8) when compared to patients with residual tumor (n = 3). This difference was, however, statistically not significant (p = 0.17). Facial nerve results did not significantly differ between near or subtotal resections when controlling for age or tumor size (p = 0.06).

Table 4. Facial nerve function in relation to residual tumor on MRI (n = 50).

	Grades I-II	Grades III-IV	Grades V-VI	
Residu	20	3*	0	23
No residu	19	8*	0	27
Total	39	11	0	50

*p = 0.17.

MRI documented growth of residual tumor

In 40 of 50 patients, a second follow-up MRI was performed (mean, 29 mo; SD, ± 9; range, 15-51 mo). In 10 of the 50 patients, there was no indication for a second MRI because the initial resection was estimated as complete and the first MRI showed no residual tumor. Of the 40 patients, 23 had residual tumor on the first MRI, and the other 17 had no residual tumor on the first MRI. Twenty patients with residual tumor on the first MRI could be followed on a second MRI, and 3 were lost to follow-up due to death (n = 2; both not VS related), and 1 patient refused follow-up imaging. For these 20 patients with residual tumor on first MRI, 18 showed no change on

the second MRI. In 2 patients, outgrowth of residual disease was observed at a mean of 36 months after surgery (SD, ± 9; range, 30-42 mo). In these patients, the residual disease had a linear-nodular configuration and was located at the brainstem (according to the Kanzaki classification). One patient was lost to follow-up before a third MRI scan could be made. In the remaining 17 residual tumor patients, a third MRI scan could be performed (mean, 49 mo; SD, ± 17; range, 28-94 mo), of which 16 showed no change. One patient clearly demonstrated outgrowth at 28 months postoperatively after an initial subtotal resection. The residual disease had a single nodular configuration that was located just outside the meatus and along the facial nerve. In the 17 patients who had no residual tumor on the first MRI, no growth could be detected on the second MRI.

As a result MRI documented outgrowth of residual tumor was observed in 3 (6%) of the 50 patients and after a follow-up of 4 years.

Postoperative complications

As shown in Table 5, postoperative complications occurred in 15 patients. There were no deaths related to the TL surgery, and most complications were transient. Cerebrospinal fluid (CSF) leakage was most frequently observed (n = 10), and most of these patients were treated with a lumbar drain. Three of these had to be treated for bacterial meningitis. In 5 patients, transient neurological complications occurred such as peroneal nerve apraxia, ataxia, or transient cranial nerve paresis.

Table 5. Postoperative complications (n = 15)*.

Complication	No. of patients
CSF leakage treated with lumbar drainage	8
CSF leakage treated with revision surgery	1
CSF leakage treated conservatively	1
Transient neurologic dysfunction	5
Bacterial meningitis	3
Postoperative hematoma requiring surgical drainage	2
Decubital ulcers	2
Sigmoid sinus thrombosis	1
Acute Respiratory Distress Syndrome	1

* Some patients experienced more than 1 complication.

Discussion

This study evaluated the results of surgical treatment of large VS with a focus on the amount of postoperative residual tumor and facial nerve outcome. The preoperative surgical strategy was to obtain complete tumor removal in all cases. This strategy was intraoperatively abandoned when strong tumor adhesions with brainstem and/or cranial nerves were encountered. In these instances, the surgeon decided to leave some tumor remnant behind so as not to jeopardize cranial nerve function. Overall, this surgical strategy resulted in removal that could be divided in 3 groups. Complete resection was obtained in 26% of the patients. In the 74% of patients in which tumor was left in situ, 58% was classified as near-total resection and 16% as subtotal resection. Interestingly, contrast-enhanced MRI 1 year postoperatively showed residual tumor in only 46% of patients. MRI did not show residual disease in the group that was surgically judged as complete resection. Apparently, in this group, the surgeon could reliably estimate whether the removal was complete or incomplete. All of the tumor remnants in the subtotal group were detected on MRI. Only the surgical assessment in the near-total group did not match the postoperative MRI images. Surprisingly, in approximately half of the patients in the near-total resection group, tumor remnants could not be dectected on MRI. This remained so on follow-up imaging. Surgical assessment in the near-total resection group in this respect was therefore too pessimistic.

Compared to MRI documentation, in about the other half of the tumors that were intraoperatively estimated as near-total resection, the amount of residual tumor should have been classified as subtotal resection. The drawback of this comparison is the 2-dimensional assessment of the preoperative tumor and postoperative residual tumor. A comparison of tumor volumes would have been more accurate, but such data could not be generated from our MRIs (17). However, we feel that our main conclusion will not be majorly affected by this drawback.

We hypothesize that in approximately half of the patients with near-total resections, postoperative tumor regression may have taken place. A possible explanation might be postoperative tumor necrosis after devascularisation. Residual remnants have been shown to be relatively avascular in VS managed with staged tumor resection (18).

At the consensus meeting on VS (2001), it was proposed that the intraoperative assessment of the extent of removal lacks objectivity, and that residual tumor should

be documented with MRI. Sofar, the surgeon's estimation of completeness of tumor removal still holds as the gold standard in the recent literature and not the objective gadolinium-enhanced MRI documentation. For instance, both Lanman et al. (8) and Briggs et al. (6) reported an extent of resection up to 96%. In these studies, it was not clearly mentioned whether postoperative MRI assessment was performed. More recently, others did use postoperative imaging. Unfortunately, a clear picture of the amount of residual tumor was not provided. In addition, imaging methods were not clearly described, and time intervals between surgery and imaging were not given (9,19-21).

Compared to other reports on the surgical treatment of large tumors, we achieved comparable facial nerve outcome (78%; H-B Grades I-II) (18-24). The size of the tumor and the surgeon's experience are pre-operative predictors for postoperative facial nerve function. The outcome of facial nerve function in our series appeared not to be related to initial tumor size. Moreover, no significant difference in facial nerve outcome was found between the subtotal or near-total resection groups. When residual tumor was left behind, facial nerve outcome was more favorable. This relationship was, however, not statistically significant. Park et al. (22) reported a preserved facial nerve outcome in 78% of cases after surgery for large VS and found an inverse correlation between facial nerve preservation and the extent of removal. Bloch et al. (23) reported favorable facial nerve outcome (H-B Grades I-II) in 81% of patients after incomplete VS resection. Postoperative MRI in their series showed that 20% of near-total and 80% of subtotally operated patients had visible residual disease. According to the authors, the absence of residual tumor in the subtotal resection group was caused by tumor regression due to devascularisation of the tumor remnants. However, the surgeon's intraoperative assessment regarding the extent of the removal might have been too pessimistic, as was the case in our series. Raftapoulos et al. (24) also performed MR imaging after surgery for large VS in order to assess their rate of tumor removal and found residual tumor in 31% of cases with preserved facial nerve function in almost all patients. In our opinion, preservation of facial nerve function is not primarily related to tumor size. We think that the vulnerability of the facial nerve is especially related to the course it takes over the tumor capsule, whether the nerve is stretched out and whether it is anatomically recognizable or only by stimulation.

To clearly distinguish actual residual tumor from dura mater inflammation or postoperative scar tissue, we described the configuration of the residue. In 4 of

the 27 patients, a linear configuration was observed within the IAC. Because of this configuration, we did not consider it as residual tumor. The dural enhancements observed in these 4 patients remained unchanged even after a follow-up of more than 3 years. The other (nodular) configurations corresponded with residual tumor and were localized near the brainstem or just outside the meatus along the facial nerve.

Recurrence was defined as MRI-documented outgrowth of residual tumor and was observed in 3 patients (6%) after a follow-up of more than 4 years. Of these patients, 2 had initially been operated subtotally, and 1 patient near-total. Two patients underwent reoperation mainly because their growing residue was linear-nodular and localized near the brainstem.

The presence or absence of tumor remnants after surgery is a major outcome measure. In this series, it appears that adequate intraoperative assessment of the extent of resection was very difficult, especially in the near-total resected tumors. Postoperative MRI to objectively measure the extent removal is therefore needed.

Conclusion

In this study, the preoperative surgical intention was to achieve complete tumor removal in large VS with preservation of facial nerve function. Magnetic resonance imaging-documented residual disease was observed in 46% of patients. In most patients, the residual tumor had a linear-nodular configuration and was located near the brainstem. Tumor control could be obtained in 94% of the patients. Recurrence mostly occurred in patients after subtotal resections with a linear-nodular configuration of the residual tumor localized at the brainstem. Postoperative facial nerve function was H-B Grades I to II in 78% of the patients. A trend between absence or presence of residual tumor and facial nerve function was observed; however, statistically not significant. Intraoperative assessment of the amount of residual tumor did not correlate well with the amount of residual tumor on the MRI scan. Postoperative residual tumor documentation should always be performed to provide a basis for assessment of recurrent disease and for interpretation of functional outcome.

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Chapter 8

General discussion and conclusion

The overall aim of this thesis was to examine the outcomes of current treatment options for vestibular schwannoma (VS) with an emphasis on patient reported outcomes (PROs). First, we described quality of life (QoL) outcome, illness perceptions (IPs) and coping behavior in patients with VS at diagnosis. Secondly, we investigated QoL and important clinical aspects in patients with VS who were treated either with wait and scan, microsurgery or radiosurgery.

Nowadays, major technical advances have ensured that the treatment of VS no longer involves life saving surgery but rather prophylactic management of future morbidity in most patients. As part of these advances, relatively new treatment options have evolved such as a wait and scan policy or stereotactic irradiation (1-12). However, the diversity in available options does not necessarily facilitate the choice of treatment. Microsurgery implies that a patient has to undergo major skull base surgery for tumor removal with significant risk of morbidity including facial nerve palsy and hearing loss, while radiosurgery is non-invasive and aims at tumor control. Radiosurgery further carries less risk of cranial nerve deficit, while conservative treatment generally implies tumor surveillance until tumor progression is observed. As a result, all current options have completely different treatment goals and criteria of success. Moreover, VS patients increasingly have their own priorities regarding treatment. Each treatment therefore, may have entirely different consequences for the life of VS patients. From this point of view, PROs such as QoL may provide valuable information in addition to the traditional outcome measures. Recently, it was also recognized that besides these conventional measures, psychological factors could play an important role in determining the patient's QoL (13-15).

In this thesis, we could not identify significant relationships between conventional measures and QoL outcomes.

For instance, deterioration of hearing loss was most reported, but this did not seem to meaningfully interfere with QoL (Chapters three and four). This could be explained by the fact that the majority of symptoms were already present before treatment or that patients gradually adjusted to them over time due to response shift (16).

Although dizziness and especially vertigo are not a common symptom in VS, they are recently thought to be predictive in QoL perception (17). We did not observe such strong relationships, but results from Chapter five showed that QoL was impaired in VS patients with vertigo to such a degree that finally microsurgery was chosen. This study has very well displayed that impaired QoL can be a decisive factor in

VS treatment. Hence, in VS patients with disabling symptoms such as vertigo, QoL assessment is crucial to further optimize VS treatment.

Tinnitus is the second most frequent symptom in VS and its development after treatment is generally thought to be unpredictable, but a slight overall increase has been observed. Tinnitus developed in a small number of conservatively treated patients, but without significant impact on QoL (Chapter three). After radiosurgical treatment, inverse correlations were found between tinnitus and the physical domains of QoL (Chapter four). Apparently, tinnitus may affect QoL in VS patients to some degree, but it is limited to daily physical tasks. Patients did not experience any emotional handicap from tinnitus, as frequently has been described (18).

In patients with facial nerve deficit or trigeminal symptoms, reduced QoL scores were observed compared to other VS patients, but differences were not significant (Chapter three and four). There has been some inconsistency with regard to the effects of facial nerve impairment on QoL after treatment for VS. Some studies report a significant negative effect on QoL, whereas others do not (19-21). A possible explanation might be the use of the SF-36 which has slight limitations with respect to otolaryngologic interventions (22,23). The use of an additional disease- or symptom-specific questionnaire could prevent these kinds of problems.

In Chapter six, we demonstrated that patients with facial nerve palsy actually experienced significant functional and psychological morbidity. A disease-specific measure, the Facial Disability Index (FDI) was used to rate impact of patients' facial function on QoL, which was significantly impaired. After facial-hypoglossal nerve transfer surgery, most patients experienced functional oral sphincter musculature and sufficient eye closure to prevent any eye problems. In addition, tongue function was preserved in all patients and no tongue atrophy was observed. Despite the small number of patients, we found significantly better QoL afterwards. It was the first report in which QoL was assessed after rehabilitative facial-hypoglossal nerve surgery.

Although it is generally known that patients with larger tumors experience increased tumor-related morbidity, we found that QoL did not differ between patients with small or large tumors. For instance, in the microsurgical treatment of large VS, tumor excision carries increased risk of facial nerve paralysis. To preserve facial nerve function and maintain patients' QoL, the surgeon may therefore leave some tumor in situ. In Chapter seven we hypothesized that postoperative facial nerve function should be significantly better when tumor is deliberately left behind.

We found that when residual tumor was left behind, facial nerve outcome was more favorable. This relationship, however, was not statistically confirmed, probably due to the small sample. In our center, facial nerve outcomes after surgery were favorable and comparable to the results from renowned clinics (24-27).

From the abovementioned results, it appears that QoL is not merely determined by the size of the VS or concomitant symptoms but may also be influenced by the burden of suffering from the disease itself. Therefore, we also explored whether psychological factors may contribute to QoL in VS patients (Chapter two). In an untreated VS patient sample, a poor active and passive coping style was observed compared to other patient groups. In general, patients were shown to perceive their tumor as an acute and life-threatening illness. Consequently, in this patient sample QoL was found to be impaired compared to norms and other comparable patient populations, which corresponds to previous data (17). However, QoL was measured before treatment and patients might not yet have been able to understand the consequences of their illness. Nevertheless, the results are important and have implications for clinicians as well as for the patient's caretakers.

Now, we can conclude that QoL in VS patients mostly depends on how they perceive their illness and to what extent they cope with it. The effects of conventional measures such as tumor size and symptoms on QoL are limited, which is in line with previous published data (28-38).

For future research, we may be able to improve QoL by an intervention in the field of IPs, as recently described in cardiac patients (39). Our patients could be referred to a medical psychologist, who could then assist them in adapting to their VS.

The results of Chapter two are highly relevant when exploring QoL for current treatment in VS, because baseline data were provided for comparison of QoL outcomes between patients either treated conservatively or with microsurgery or radiosurgery. When compared to the untreated patient sample from Chapter two, improvement of QoL was observed for all three treatment modalities. We hypothesize that after treatment, VS patients experienced their illness as being 'controlled' or cured and without significant morbidity. In contrast, the tumors of the patients in Chapter two were not treated yet.

The results of our observational study (Chapter three) were encouraging, because in the past, the presumed impact of a wait and scan policy on QoL has generally been used as an argument to proceed to microsurgery. So far, there has been a paucity on the QoL subject in conservative treatment of VS. Our data were prospectively

collected over a period of almost four years, which is unique when reviewing the current literature. However, follow-up is still short given the slow growing character of VS. Our study failed to assess QoL in the entire observed cohort, which may limit the interpretation of these data. However, in a recent study, QoL was not found to be further impaired in VS patients who had failed conservative treatment (40). As in our study, others also reported on stable QoL in observed VS patients, but without the use of baseline and posttreatment data (41). In our opinion, therefore, we have provided strong evidence that a wait and scan policy does not adversely affect QoL in VS patients.

Despite the favorable outcome of our radio- and microsurgical samples, QoL of these patients was still impaired when compared to their control samples. While radiosurgical treatment of VS is less invasive than microsurgery, it may still induce several complaints such as hearing loss, tinnitus, decrease of facial nerve function, facial pain and dysbalance. Complications of radiosurgery have also been reported, although the consequences for patients are often less serious compared to complications after microsurgical treatment. In those patients who experienced complications in our studies, a significant QoL impairment was not observed. One possible explanation might be that complications were often transient and in a small number of patients. Moreover, QoL was generally assessed some time after treatment.

The QoL outcomes of the operated patients were comparable to the radiosurgically as well as the conservatively treated VS patients. From a QoL point of view, the three patient groups did not seem to differ significantly, although there are major differences in terms of patient and tumor characteristics. Our results were confirmed by a recent prospective study using the SF-36 measure at regular intervals, which also concluded that there were no QoL differences between the three current modalities (42).

Throughout our studies, we have used validated generic questionnaires to measure QoL. However, for optimal QoL assessment, we recommend the use of generic measures in combination with disease- or symptom-specific measures as described in Chapter five. Our methods consisted of solid QoL instruments, but for future research, it would be preferable to use a VS-specific questionnaire in addition to those currently used. Such a questionnaire could focus more on the particular problems encountered when suffering from VS. However, no validated VS-specific measure exists so far.

The results of this thesis have led to a more conservative approach for VS patients in our department. Nowadays, an initial wait and scan policy for our patients with small- or medium-sized tumors is increasingly adopted. In case of tumor progression or increase of symptoms, active treatment is offered to these patients. At the LUMC, microsurgery is generally offered to patients with growing tumors depending on patient and tumor factors. As recognized by others, microsurgery is also our first choice in the treatment of large tumors. However, from our research and from published reports world-wide, we are convinced that radiosurgery has become a well-established treatment option for VS next to microsurgery.

Our study did not aim to compare outcomes of the different modalities in order to claim 'the best treatment option for VS'. In our opinion, there is no clear option of what would be best for all individuals and it would not even be possible to conclude this from our studies. Given our results, and the state-of-the-art with regard to the medical management of patients with VS, it can be concluded that future research should focus on a number of issues. First, the development of a specific QoL measure for patients with VS would be helpful. Secondly, a head to head comparison of the treatment modalities for patients with VS would shed light on crucial questions about which treatment is best for which patients, taking QoL into account. Thirdly, further research should focus on developing self-management interventions in patients with VS, most likely with the inclusion of partners of the patients, and with QoL as the central outcome measure. VS is an area with exciting research and clinical challenges. This thesis has attempted to contribute to the area.

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Summary and concluding remarks

Vestibular schwannomas are benign intracranial tumors which generally arise from the Schwann cells of the superior part of the vestibular portion of the eight cranial nerve. The most common symptoms accompanying vestibular schwannoma (VS) are unilateral hearing loss, tinnitus, vertigo and unsteadiness. For many years, microsurgical treatment of VS has been considered the 'gold standard'. However, the treatment of VS continues to evolve with the advent of alternative treatment options such as wait and scan and stereotactic irradiation. Moreover, advances in MRI techniques have allowed for an early diagnosis and exact measurement of growth, which has led to an increased number of patients with small and minimally symptomatic tumors. As a result, the treatment of VS no longer involves life saving surgery, but prophylactic management of future morbidity. These developments have also created new insights into how vestibular schwannoma can be best treated, as it has become clear that the tumor may remain unchanged for many years. However, the treatment of VS patients still remains a matter of debate with advocates and opponents of each modality. Traditionally, the evaluation of VS treatment was performed using primary outcome measures such as mortality and morbidity. But the subject of quality of life (QoL) has increasingly become an important outcome measure in VS. QoL may provide clinicians valuable information that is not always supplied by traditional outcome measures. This thesis describes how VS patients perceive their QoL at diagnosis and further explores QoL and outcomes in patients treated with observation, microsurgery or radiosurgery.

Chapter one gives a general introduction with a short review of the current options and patient's perceptions and describes treatment outcomes in VS. At the end of this chapter, the aim and outline of the study are delineated.

In **Chapter two** QoL outcome, illness perceptions (IPs) and coping behaviour in VS patients at diagnosis are presented. To assess IPs and coping behaviour, the Illness Perception Questionnaire - Revised (IPQ-R) and Utrecht Coping List (UCL) were used. QoL was measured using the SF-36, a validated generic QoL measure. A prospective analysis in 79 patients with small- and medium-sized VS demonstrated that IPs and coping, but especially QoL in VS patients, were not as good as reference values. Untreated VS patients also showed to have poor active and passive coping styles and seek less social support compared to other patients. The results from this study indicate that VS patients are a group of patients that suffer from the moment of their diagnosis. This may have implications for clinical decision making and for optimizing

interaction with patients. Changing IPs and coping by means of an intervention may improve QoL in VS patients.

Chapter three investigates how the tumor, the cardinal symptoms, and QoL developed during follow-up in wait and scanned VS patients. A total of 70 vestibular schwannoma patients who were initially included in the wait and scan protocol were followed with a mean observation time of 43 months. All patients had small- or medium-sized tumors when they were included in the protocol. QoL was measured at diagnosis and at the end of follow-up in those patients who were still conservatively treated and by using the SF-36. The study group was characterized by non-growing small tumors and relatively stable symptoms over time. We found that conservative observation did not significantly affect QoL in these patients. Most of the tumors did not grow and useful hearing was preserved in more than half of the patients with useful hearing. Initial conservative observation is therefore a safe option for patients with smaller tumors. There was no significant relationship between cochleovestibular symptoms and QoL. However, progression of hearing loss was observed during follow-up. Patients should be counseled regarding this risk before treatment.

Chapter four retrospectively reports on QoL and important clinical aspects in VS patients after radiosurgery. Seventy-two consecutive, newly-diagnosed patients with unilateral VS underwent linear accelerator-based radiosurgery with marginal tumor doses of 1 x 12 Gy. A total of 64 patients filled out the SF-36 questionnaire and scores of these patients were compared with SF-36 scores of the general sample. Local tumor control and symptoms were also studied. The results showed favorable tumor control rates and low posttreatment morbidity after a mean follow-up of 34 months. In general, few patients reported progression of symptoms and QoL did not significantly correlate with any of these symptoms. After treatment, QoL scores were moderately affected when compared to norms. It was concluded that QoL after radiosurgical treatment for VS was impaired. Radiosurgery offered good tumor control and favorable clinical outcome similar to other published reports. This report is one of the few studies that describe QoL in VS patients after low dose radiosurgery. The results may be valuable when counseling patients with small- or medium-sized VSs, for which a radiosurgical treatment has increasingly become a treatment option.

Chapter five determines the impact of translabyrinthine (TL) surgery on QoL in VS patients with disabling rotatory vertigo. A total of 18 patients with a unilateral intracanalicular VS, without serviceable hearing in the affected ear and severely handicapped by attacks of rotatory vertigo were prospectively studied. Despite an

initial conservative treatment, extensive vestibular rehabilitation exercises, TL surgery was performed because of the disabling character of the vertigo. Preoperative and postoperative QoL was measured using the SF-36 and DHI. Preoperative QoL was reduced because of the disabling vertigo, but significantly improved after TL surgery. However, QoL was still reduced when compared to the general sample. Until now, evidence for other possible treatment options such as (chemical) labyrinthectomy or radiosurgical treatment in these patients is limited. From our study, it may be concluded that TL surgery significantly improved the patients' QoL and surgical treatment should be considered in patients with small- or medium-sized tumors and persisting disabling vertigo.

In **Chapter six**, we used a new variation of the facial-hypoglossal nerve coaptation to reanimate the paralyzed facial musculature after (surgical) trauma. With this technique 1.5 to 2 cm of the facial nerve is freed from its canal in the mastoid bone to perform a direct coaptation to a restricted part of the hypoglossal nerve. The technique avoids the use of a graft and is thereby a safer procedure because there is only one nerve coaptation site. This factor reduces the potential risk of failure of the reconstructive procedure caused by dehiscence. Another advantage compared to other facial-hypoglossal techniques is that the hypoglassal nerve is only partly incised which reduces the risk of hemiglossal paralysis or hemitongue atrophy. Facial nerve outcome was evaluated using the House-Brackmann grading system, which is widely used by surgeons to grade facial nerve function, but also using the Facial Disability Index (FDI), a frequently used QoL questionnaire related to facial nerve function.

In the majority of our patients, we achieved the main goals of rehabilitative facial surgery: functional oral sphincter musculature and sufficient eye closure to prevent any eye problems. In addition, tongue function was preserved in all patients, and no tongue atrophy was observed. Clinical and QoL outcomes of our technique were similar to published results by other authors. Functional improvements were reported while eating, drinking, or closing the eye, and fewer social limitations related to their facial function were observed.

In **Chapter seven** we hypothesized that postoperative facial nerve function should be significantly better when tumor is deliberately left behind during VS surgery. Second, we aimed to objectively assess the extent of the removal using gadolinium-enhanced MRI scans and compared results with the extent of the removal as intraoperatively estimated by the surgeon. A total of 51 patients with

large VS were operated using the TL approach. The extent of the resection was intraoperatively estimated as complete, near, and subtotal. The amount of residual tumor was measured, and the shape and localization was scored on gadolinium-enhanced magnetic resonance imaging (MRI). Potential growth of residual tumor was documented with frequent MRI follow-up. Postoperative facial nerve function was classified according to the House-Brackmann classification. Tumor control with good facial nerve function could be obtained in most patients. A trend was observed that facial nerve outcome was more favorable when residual tumor was left behind. Intraoperative assessment did not correlate with the amount of residual tumor on postoperative MRI. Objective documentation with postoperative contrast-enhanced MRI to measure the extent of removal is always recommended.

Chapter eight comprises the main conclusions and general discussion of the results described in this thesis. Furthermore, clinical implications and future directions of research are discussed.

Finally, with regard to the aims of the study, we may conclude that more insight was provided into patients' perceptions and outcomes in the treatment of VS. Previous knowledge on QoL outcome in the treatment of VS patients was confirmed and new information such as illness perceptions and coping behaviour was added. In general, patients with VS suffer from an impaired QoL and treatment will not necessarily restore the patient's quality of daily life. At present, the choice of treatment in VS is still a matter of debate and probably will remain so for a number of reasons. One of the principal precepts of medicine "primum non nocere", first do no harm, should be kept in mind by both clinicians and patients when discussing the treatment options of VS. The major results of this study can make a valuable contribution to clinical decision making and further optimize management of VS. With awareness regarding this topic, we can help to further elucidate QoL perception and try to improve QoL in VS patients in the future.

Samenvatting

Vestibularis schwannomen zijn goedaardige hersentumoren die meestal uitgaan van de Schwann cellen van de nervus vestibularis superior. De meest voorkomende symptomen van het vestibularis schwannoom (VS) zijn eenzijdig perceptief gehoorverlies, tinnitus en/of evenwichtsklachten. Gedurende vele jaren is microchirurgische behandeling van de tumor beschouwd als gouden standaard in de behandeling van het VS. Er is echter ook een aantal nieuwere, alternatieve behandelopties voor het VS zoals wait and scan of radiochirurgie. Nieuwe ontwikkelingen op het gebied van de MRI zorgen ervoor dat de diagnose steeds sneller gesteld kan worden en tumorprogressie beter kan worden vastgelegd. Hierdoor is er een toenemend aantal VS patiënten met kleinere en vaak asymptomatische tumoren. Dankzij deze vooruitgang bestaat de behandeling van het VS vaak niet meer uit een levensreddende operatie, maar meer uit een profylactisch beleid voor toekomstige morbiditeit. De keuze van behandeling blijft echter onderwerp van discussie met voor- en tegenstanders van elke modaliteit. Het is gebruikelijk dat in de evaluatie van de behandeling van een VS, de primaire uitkomstmaten zoals mortaliteit of morbiditeit worden gebruikt. Het onderwerp kwaliteit van leven (KvL) speelt echter een steeds grotere rol in de evaluatie van de behandeling. Het blijkt dat KvL clinici informatie kan geven die niet altijd met de gebruikelijke uitkomstmaten kan worden bepaald. Dit proefschrift beschrijft KvL tezamen met enkele belangrijke klinische aspecten in patiënten met een VS op het moment van de diagnose en na behandeling met wait and scan, micro- of radiochirurgie.

In **hoofdstuk 1** wordt een algemene introductie gegeven met een kort overzicht van de verschillende behandelopties waarna de percepties van de patiënt en uitkomst van behandeling van het VS aan bod komen. Aan het eind van dit hoofdstuk wordt het doel van de studie behandeld.

Hoofdstuk 2 behandelt de KvL, ziektepercepties en het copinggedrag van patiënten met een VS op het moment van de diagnose. De ziektecognities en het coping gedrag worden gemeten met twee vragenlijsten: de Illness Perception Questionnaire (IPQ-R) en de Utrechtse Coping Lijst (UCL). De algemene KvL werd gemeten met behulp van de gevalideerde SF-36. In een prospectieve analyse van 79 patiënten met een klein tot middelgroot VS, werd aangetoond dat ziektecognities, coping en met name KvL in patiënten met een VS duidelijk verminderd waren in vergelijking met de referentiewaarden. Onbehandelde patiënten met VS hadden ook verminderde actieve en passieve coping mechanismen en zochten minder sociaal contact in vergelijking met andere patiënten. De resultaten van deze studie

tonen aan dat patiënten met een VS vanaf het begin van de diagnose lijden onder hun ziekte. Deze bevindingen kunnen van invloed zijn op de beslisvorming en op het optimaliseren van contact met patiënten. Verder zou het veranderen van de ziektecognities en het copinggedrag door middel van een interventie de KvL in deze patiënten kunnen verbeteren.

Hoofdstuk 3 beschrijft het natuurlijk beloop van de tumor met begeleidende symptomen en de ontwikkeling van de KvL gedurende follow-up in een wait and scan populatie. Een groep van 70 patiënten werd initiëel geïncludeerd in het wait and scan - protocol en vervolgd gedurende gemiddeld 43 maanden. Tijdens de inclusie in het protocol hadden alle patiënten een kleine tot middelgrote tumor. De KvL werd met behulp van de SF-36 gemeten aan het begin van de observatieperiode en aan het eind in de patiënten die nog steeds geïncludeerd waren. De bestudeerde patiënten hadden allemaal kleine, niet groeiende tumoren met relatief weinig progressie van symptomen gedurende de periode. Uit onze resultaten blijkt dat conservatieve behandeling van deze patiënten de KvL niet significant beïnvloedde. In de meeste tumoren was er geen sprake van progressie en het bruikbaar gehoor werd gespaard in meer dan de helft van de patiënten met een bruikbaar gehoor. Een initiële afwachtende behandeling is daarom een veilige behandeling voor patiënten met kleinere tumoren. Verder werd er geen significante relatie gevonden tussen begeleidende symptomen en KvL. Tijdens follow-up werd wel progressie van het gehoorverlies gemeten. Patiënten moeten hierover worden ingelicht voorafgaande aan de behandeling.

Hoofdstuk 4 behandelt een retrospectieve studie over KvL en enkele belangrijke klinische aspecten van radiochirurgie uitgevoerd met de lineaire accelerator. In totaal werden 72 nieuwe VS patiënten met een unilateraal VS behandeld met lineaire accelerator radiochirurgie met marginale dosis van 12 Gy. Uiteindelijk werd de SF-36 door 64 patiënten ingevuld en de scores vergeleken met de referentie populatie. Lokale tumor controle en symptomen werden ook bestudeerd. De resultaten lieten zien dat er een goede tumor controle en weinig morbiditeit is na een follow-up van 34 maanden na behandeling. Weinig patiënten rapporteerden een toename van symptomen, waarbij geen significante relatie werd gevonden met de KvL. Na radiochirurgische behandeling waren de KvL scores iets lager dan de scores van de normpopulatie. Er kan worden geconcludeerd dat patiënten na radiochirurgie een verminderde KvL hebben ten opzichte van een normaal populatie. Radiochirurgie biedt goede klinische uitkomst, welke vergelijkbaar is met andere studies. Deze studie

is een van de weinige studies die over KvL rapporteert na low dose radiochirurgie. Het resultaat van deze studie is dan ook van belang bij het informeren van patiënten met kleinere of middelgrote tumoren, waarvoor radiochirurgie steeds vaker de keuze van behandeling wordt.

Hoofdstuk 5 richt zich op het effect van translabyrinthaire (TL) brughoekchirurgie op de KvL in patiënten met een VS en invaliderende duizeligheidsklachten. In totaal werden 18 patiënten met een unilateraal intracanaliculair VS met onbruikbaar gehoor aan de tumor zijde en invaliderende aanvalsgewijze duizeligheid prospectief bestudeerd. Na initieel conservatief behandeld te zijn met uitgebreide vestibulaire oefentherapie, werden patiënten uiteindelijk geopereerd via de TL benadering omdat de invaliderende duizeligheid persisteerde. De preoperatieve en postoperatieve KvL werd gemeten met behulp van de SF-36 en DHI. De preoperatieve KvL was verminderd door de invaliderende duizeligheidsklachten, maar verbeterde sterk na TL operatie. Maar de KvL was na operatie nog steeds minder dan de KvL van onze referentie populatie. Tot nu toe is er weinig ander bewijs over alternatieve behandelingen zoals een chemische labyrintectomie of radiochirurgische behandeling. Uit de resultaten van deze studie blijkt dat microchirurgische behandeling via de TL approach, een duidelijke verbetering geeft van de KvL in deze patiënten. Microchirurgische behandeling moet worden overwogen in patiënten met kleine en middelgrote tumoren met blijvende invaliderende duizeligheid.

In **hoofdstuk 6** wordt een nieuwe methode van de facialis-hypoglossus coaptatie (FHT) beschreven om aangezichtsverlamming na (chirurgisch) trauma te verhelpen. Met behulp van deze techniek wordt de nervus facialis vrijgelegd uit het mastoid over een traject van 1,5 tot 2 cm om zo een directe coaptatie te maken met een deel van de nervus hypoglossus. Deze techniek vermijdt het gebruik van een graft en is daarom een veilige techniek omdat er in principe maar één coaptatie plaats is. Hierdoor wordt het risico op falen van de reconstructie door dehiscentie verminderd. Een ander voordeel in vergelijking met andere FHT is dat de nervus hypoglossus maar gedeeltelijk wordt geïncideerd waardoor de het risico op halfzijdige verlamming of atrofie van de tong verminderd is. De functie van de nervus facialis wordt niet alleen gescoord met behulp van de House-Brackmann classificatie, welke veel gebruikt wordt door chirurgen, maar ook via de Facial Disability Index (FDI). Deze questionnaire is gerelateerd aan de functie van de nervus facialis. In bijna alle patiënten, hebben we de doelen van dynamische facialis reconstructie bereikt: een functionerende mondmusculatuur en voldoende sluiting van het oog om oog

problemen te voorkomen. Ook de tongfunctie werd gespaard in alle patiënten en er was geen atrofie van de tong. De klinische en KvL uitkomsten van onze techniek kwamen overeen met andere resultaten. Er werden functionele verbeteringen bij eten, drinken en het sluiten van het oog gerapporteerd en minder sociale beperkingen als gevolg van de nervus facialis functie.

In **hoofdstuk 7** stelden we dat de postoperatieve nervus facialis functie beter zou moeten zijn als residu tumor wordt achtergelaten op de nervus facialis tijdens de operatie. Ook was het doel om de mate van resectie objectief te bepalen met behulp van een MRI met gadolinium als contrastmiddel waarbij de resultaten dan vergeleken werden met de peroperatief ingeschatte mate van resectie door de chirurg. In totaal werden 51 patiënten met grote tumoren geopereerd via de TL benadering. De mate van resectie werd intraoperatief ingeschat als compleet, 'near' en subtotaal. De hoeveelheid residu tumor werd gemeten en de omvang en lokalisatie werd gescoord op de MRI met contrast. Eventuele uitgroei van residu werd gedocumenteerd door herhaalde MRIs tijdens follow-up. Postoperatieve nervus facialis functie werd geclassificeerd volgens de House-Brackmann classificatie. Een goede tumor controle en nervus facialis functie werd bereikt in het merendeel van de patiënten. Er werd een trend gezien dat de nervus facialis uitkomst verbeterde in geval van residu tumor. De intraoperatieve inschatting kwam niet overeen met de hoeveelheid residu op de postoperatieve MRI. Objectieve documentatie van de mate van resectie met behulp van MRI met contrast wordt altijd aangeraden.

Hoofdstuk 8 bevat de belangrijkste conclusies en de discussie van de resultaten in dit proefschrift. Verder worden een aantal belangrijke implicaties voor de klinische praktijk en voor vervolgonderzoek gegeven.

Gezien de resultaten van het in dit proefschrift beschreven onderzoek kan worden geconcludeerd dat er meer inzicht is verkregen in de perceptie van de patiënt over de aandoening en ten aanzien van uitkomsten van behandeling van het VS. De eerder opgedane kennis van KvL in de behandeling van het VS kon worden bevestigd en nieuwe informatie zoals over ziektecognities en coping gedrag werd toegevoegd aan bestaande literatuur. Het blijkt dat patiënten met een VS over het algemeen een verminderde KvL ervaren en dat behandeling niet hoeft te leiden tot een herstel van KvL. Op dit moment is de keuze van behandeling nog steeds onderwerp van discussie wat waarschijnlijk ook nog zo zal blijven door verschillende redenen. Een van de belangrijkste stelregels in de geneeskunde 'primum non nocere', oftewel in ieder geval geen kwaad doen, moet in gedachte worden gehouden door zowel clinici

als patiënten wanneer de behandelingsopties voor het VS worden besproken. De belangrijkste resultaten van deze studie kunnen een waardevolle aanvulling zijn voor de klinische besluitvorming en het optimaliseren van het overleg met de patiënt met een VS. Een beter besef van het onderwerp kan helpen de perceptie van de KvL in patiënten met een VS te verklaren en mogelijk in de toekomst ook te verbeteren.

Curriculum vitae

The author of this thesis was born on the 28th of March 1975 in the city of Hamelen. After completing his secondary education (VWO) in 1994, he started his medical studies at the University of Leiden and obtained medical qualification in 2002. The research which resulted in this thesis was initiated in 2001. In 2003, he commenced his ENT-residency at the Leiden University Medical Centre which he completed in May 2009. Shortly, he will commence his fellowship Facial Plastic Surgery at the Diakonessenhuis Utrecht / Zeist / Doorn, where he currently works as Chef de Clinique.